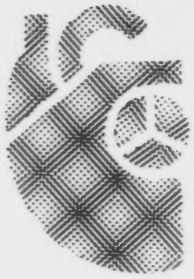
NOV 19 '84

HE20.3202:C76/984

TES
L47



Devices and Technology Branch Contractors Meeting 1984

159

ORIGINAL

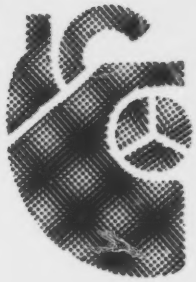
Program

December 5, 6 and 7, 1984

Division of Heart and
Vascular Diseases
National Heart, Lung, and
Blood Institute

AG

BEST COPY AVAILABLE



Devices and Technology Branch Contractors Meeting 1984

Program

Division of Heart and
Vascular Diseases
National Heart, Lung, and
Blood Institute

December 5, 6 and 7, 1984

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

BEST COPY AVAILABLE

I

BLANK PAGE

Table of Contents

BEST COPY AVAILABLE

BLANK PAGE

TABLE OF CONTENTS

STAFF, DEVICES AND TECHNOLOGY BRANCH, DHVD, NHLBI xv

MEETING SCHEDULE OVERVIEW xvii

ABSTRACTS 1

CALCIFICATION OF PROSTHETIC MATERIALS

Prosthetic Materials in the Cardiovascular System 3
Walter E. Brown, Ph.D.; Laurence C. Chow, Ph.D.;
Branko Tomazic, Ph.D.; Naomi Eidelman, Ph.D.

Calcification Mechanisms in Cardiovascular Prostheses 4
James W. Buchanan, D.V.M., M.Sc.; Julius Melbin, V.M.D., Ph.D.;
Irving M. Shapiro, B.D.S., Ph.D.; Ellis E. Golub, Ph.D.;
Jeffrey M. Dunn, M.D.; Peter Frasca, Ph.D.

Quantification of Regional Platelet Thrombosis and Regional Calcium Mapping on Pericardial Tissue Valve Prosthesis with Diphosphonate Treatment in Calves 5
Mrinal K. Dewanjee, Ph.D.; Michael P. Kaye, M.D.;
William D. Edwards, M.D.; Paul Didisheim, M.D.;
James H. Chesebro, M.D.; Paul H. Wooley, Ph.D.;
Steven S. Barham, Ph.D.; Paul E. Zollman

Quantification of Granulocyte Deposition on Vascular Grafts in Dogs with ^{111}In-Labeled Granulocytes 7
Mrinal K. Dewanjee, Ph.D.; Michael P. Kaye, M.D.

Structural Proteins in Bioprosthetic Valve Calcification 8
Robert J. Levy, M.D.; Frederick J. Schoen, M.D., Ph.D.;
Alan C. Nelson, Ph.D.

Mechanical Etiology of Calcification 9
Param I. Singh, Ph.D.; Robert D. Cumming; Jeffrey L. Snow, B.S.;
Loyde H. Romero, M.D., Ph.D.; Neil K. Harpster, D.V.M.;
Jane B. Lian, Ph.D.

Blood-Material Interactions: Calcification 11
Jane B. Lian, Ph.D.

BEST COPY AVAILABLE

SMALL VESSEL PROSTHESES

Endothelial Cell Seeding of Small Vessel Prostheses 15
Allan D. Callow, M.D., Ph.D.

Endothelial Seeding of Vascular Grafts 16
John Glover, M.D.; Malcolm Herring, M.D.

Effects of Compliance Mismatch in Arterial Grafts 17
William A. Abbott, M.D.; Joseph Megerman, Ph.D.; John T. Fallon, M.D., Ph.D.; Jonathan Hasson, M.D.; Robert E. Baier, M.D.

Application of Arterial Regeneration 18
Howard P. Greisler, M.D.; Dae Un Kim, M.D.; John B. Price, M.D.; Arthur B. Voorhees, M.D.; Richard Raymond, Ph.D.; Philip B. Dobrin, Ph.D.

Small Diameter Vascular Prostheses 19
Klaus Brendel, Ph.D.; James M. Malone, M.D.; Raymond C. Duhamel, Ph.D.

Graft Thrombus Formation in Baboons 20
Stephen R. Hanson, Ph.D.; Laurence A. Harker, M.D.

Bioresorbable Vascular Grafts 21
Pierre M. Galletti, M.D., Ph.D.; Tin-Ho Chiu, Ph.D.; Harvey F. Sasken, M.D., M.P.H.; Peter D. Richardson, Ph.D.; Paul McMillan, Ph.D.; Leonard A. Trudell, D.Sc.

BIOMATERIALS

Physical Testing of Polymers for Use in Circulatory Assist Devices 25
Carl R. McMillin, Ph.D.

Poly(organophosphazenes) for Biomedical Uses 26
Harry R. Allcock, Ph.D.

Eyrthrocyte Deformability and Vascular Pathophysiology 27
S.P. Sutera, Ph.D.; R.A. Gardner, Ph.D.; J.R. Williamson, M.D.

Flow Effects on Leukocyte Function and Surface Adhesion 28
Larry V. McIntire, h.D.; Suzanne G. Eskin, Ph.D.; Bill Brinkley, Ph.D.

Initial Events in Thrombus Formation on Surfaces 30
Sung Wan Kim, Ph.D.; Jan Feijen, Ph.D.; Teruo Okano, Ph.D.

Cell and Protein Reaction with Foreign Materials 31
Thomas A. Horbett, Ph.D.; Buddy D. Ratner, Ph.D.; Allan S. Hoffman, Sc.D.

BEST COPY AVAILABLE

Novel Approach to Nonthrombogenic Polymer Surfaces 32
Sung Wan Kim, Ph.D.; Teruo, Okano, Ph.D.

Hemodynamics in Vascular Surgery 33
Frank W. Logerfo, M.D.; Christian Haudenschild, M.D.;
C. Robert Valeri, M.D.; Ralph C. Ito, Ph.D.

Surface-Active Antithrombotic Agents for Prostheses 34
Andrew Lasslo, Ph.D.; Marion Dugdale, M.D.

Response of Cultured Endothelial Cells to Flow 35
Suzanne G. Eskin, Ph.D.; Christopher L. Ives, Ph.D.;
Larry V. McIntire, Ph.D.; Charles L. Seidel, Ph.D.

A Molecular Level Approach to Blood Materials Interaction 36
Robert I. Leininger, Ph.D.; David J. Fink, Ph.D.;
R. Michael Gendreau, M.D.; Timothy B. Hutson;
Robert J. Jakobsen

Blood-Materials Interactions: The Bridge Problems 37
W. Jean Dodds, D.V.M.; John A. Bergeron, Ph.D.

Fate of Surface Bound Heparin 38
Michael V. Sefton, Sc.D.; Mark W.C. Hatton, Ph.D.;
Walter Zingg, M.D.

Long-Term Biodegradation of Elastomeric Biomaterials 39
P. Anne Hiltner, Ph.D.; James M. Anderson, M.D., Ph.D.

Surface and Bulk Structure of Polyetherurethanes 40
Buddy D. Ratner, Ph.D.; Amarjeev Kaul, Ph.D.

PAA Adsorption on Polymers Using TIRF and FTIR/ATR 41
Channing R. Robertson, Ph.D.

Human Vascular Grafts: The Blood/Materials Interaction 42
James M. Anderson, M.D., Ph.D.

Blood Trauma from Microporous Membrane Oxygenators 43
Robert C. Eberhart, Ph.D.; Frederick Grinnell, Ph.D.;
Morton Prager, Ph.D.; Mark Munro; Jack Frautschi

Effects of Shear Stress on Red Blood Cells 44
Mark M. Udden, M.D.

Mechanisms of Arterial Graft Failure 45
Alexander W. Clowes, M.D.; Allen M. Gown, M.D.;
Stephen R. Hanson, Ph.D.; Michael A. Reidy, Ph.D.

Anatomical Substitutes with Proclivity for Cell Lining 46
Peter H. Duquette, Ph.D.; Ruth B. Johnson, M.S.;
Peter Nash, Ph.D.

BEST COPY AVAILABLE

PRIMARY REFERENCE MATERIAL

Procurement of Primary Reference Materials 49
Robert S. Ward, Kathleen A. White

MECHANICAL CIRCULATORY SUPPORT: ENERGY TRANSMISSION

Research and Development of Systems for Transmitting Energy Through Intact Skin 53
Craig Sherman, Ben Daly

Electrical Energy Transmission Technique Development 55
Peer M. Portner, Ph.D.; Sylvain Pitzele, M.D., Ph.D.; David H. LaForge, B.S.; George F. Green, Ph.D.; Frank K. Beering, B.S.

Development of a Percutaneous Energy Transmission System 56
Adrian Kantrowitz, M.D.; Paul S. Freed, M.S.; Tarik Wasfie, M.D. Kenichi Hagiwara, M.D.; F.L. Vaughan, Ph.D.; L.I. Bernstam, M.D.; I.A. Bernstein, M.D.; Robert H. Gray, Ph.D.

Development of Percutaneous Energy Transmission Systems 57
Benedict D.T. Daly, Jr., M.D ; Kurt A. Dasse; Warren Clay; Victor L. Poirier; Christian C. Haudenschild; Richard E. Fine; William J. Robinson; James N. Ross; Michael Szycher; Michael B. Worthington; Herbert L. Kayne; Michael B. Lewis; John Handrahan

MECHANICAL CIRCULATORY SUPPORT

Development of a Thermal Ventricular Assist System (TVAS) 63
Maurice A. White, M.S.; Yukihiko Nose, M.D., Ph.D.; Robert L. Whalen, S.B.

Thermal Ventricular Assist System 64
J.C. Moise, Ph.D.; Y. Nose, M.D., Ph.D.; A.L Blubaugh, Ph.D.

Development of an Implantable, Electrically-Actuated Heart Assist System 65
O.H. Frazier, M.D.; J.A. Chambers; J.M. Fuqua, Jr.; S.R. Igo; M.G. McGee; G.E. Pool; L.A. Davies; L.M. Mahler; T.T. Yen; M.L. Gillichbauer; O.U.J. Okereke, M.D.; W.C. Clay, S.D. Buczak; G.J. Creager; S.M. Parnis

Development of an Implantable, Integrated Electrically-Powered Left Heart Assist System 66
David B. Gernes; William Bernhard, M.D.

BEST COPY AVAILABLE

Development of an Electrohydraulic Driven Left Heart Assist System 68
John Moise, Ph.D.; Yukihiko Nose, M.D., Ph.D.; Ray Kiraly, M.S.;
Luiz Fujimoto, M.D.; Leonard Golding, M.D.; Bill Smith, M.S.;
Hiroaki Harasaki, M.D., Ph.D.; Jim Payne, B.S.; Ken Butler, M.S.

Development of an Implantable Left Heart Assist System 70
P.M. Portner, Ph.D.; P.E. Oyer, M.D., Ph.D.;
J.S. Jassawalla, M.S.; J.S. Brugler, Ph.D.; A.K. Ream, M.D.;
P.J. Miller, M.S.; H. Chen, M.S.; G.F. Green, Ph.D.;
D.H. LaForge, B.S.; J. Lee, M.S.;N. Ramasamy, Ph.D.;
M.G. Conley, B.S.; F.K. Beering, B.S.;
M.E. Billingham, M.B., B.S.

Clinical Application of Ventricular Assist Devices 71
D. Glenn Pennington, M.D.; George Williams, M.D.;
Hind Bashiti, M.D.; David Lagunoff, M.D.; J. Heinrich Joist, M.D.;
John P. Merjavy, M.D.; Larry Samuals, M.D.; Marc T. Swartz

Fabrication of Cardiovascular Devices 74
David J. Farrar, Ph.D.

Left Ventricular Bypass for Myocardial Infarction 75
William S. Pierce, M.D.; Gerson Rosenberg, Ph.D.;
David B. Geselowitz, Ph.D.; Donald L. Landis; James H., Donachy;
Alan J. Snyder; William J. White, V.M.D.; G. Allen Prophet, B.S.;
Kay Holtzman

Development and Evaluation of an Artificial Heart 77
William S. Pierce, M.D.; David B. Geselowitz, Ph.D.;
Gerson Rosenberg, Ph.D.; Donald L. Landis; James H. Donachy;
Alan J. Snyder; Thomas J. Cleary; William J. White, V.M.D.;
Paul E. Beard; G. Allen Prophet

Biventricular Assist and Replacement Studies 79
Yukihiko Nose, M.D., Ph.D.; Hiroaki Harasaki, M.D., Ph.D.;
Gordon Jacobs, M.S.E.E.; Raymond Kiraly, M.S.M.E.;
Ryohei Yozu, M.D.; William Smith, M.S.M.E.;
Teriuchi Shimomitsu, M.D.

Right Heart Function with Left Heart Assist 80
David J. Farrar, Ph.D.; Peter G. Compton, M.S.;
James J. Hershon, M.D.; J. Donald Hill, M.D.

Fluid Dynamics in Transparent Natural Blood Vessels 81
Takeshi Karino, Ph.D.; Hitoshi Kinomoto, M.D.;
Yasunori Sohara, M.D.

LVAD and RVAD with Portable Electropneumatic Drive 82
Willem J K Iff, M.D., Ph.D.; George M. Pantalos, Ph.D.;
Donald B. Olsen, D.V.M.; William C. DeVries, M.D.

BEST COPY AVAILABLE

Compliance System for Implantable Blood Pumps 83
Yukihiko Nose, M.D., Ph.D.; Raymond J. Kiraly, M.S., M.E.; Hiroaki Harasaki, M.D., Ph.D.; William A. Smith, M.S., M.E.; Satoru Kaneko, M.D.

Myocardial Recovery After Acute Ischemic Heart Failure 84
Jeffrey L. Peters, Ph.D., M.D.; Clifford S. Kwan-Gett, M.D.; Kelly W. Smith, E.E., M.D.; Gregory J. Wilson, M.D.; Donald A. Mickle, M.Sc., M.D.; Alexander D. Romaschin, Ph.D.; Barry L. Bagley, B.A.; L. Steven Beck, D.V.M., M.S.; John A. Burkart, Ph.D.; Therese A. Davy, B.Sc.; George Jackowski, Ph.D.; Karla Kornmayer, M.D.; David L. Mock, M.D.; Clyde Null, M.D.; George F. Rich, M.E., M.E.B.E.; Gary R. Snider, M.D.; Elizabeth Sonne, B.Sc.; Floyd Sweat, Ph.D.

Device Readiness Testing of Implantable Ventricular Assist Systems 85
Warren Clay; William Bernhard, M.D.

Device Readiness Testing of an Electrohydraulic Ventricular Assist System 86
R.T.V. Kung, Ph.D.; P.I. Singh, Ph.D.; D.M. Lederman, Ph.D.; B.B. Adams, B.S.; W.J. Bolt, B.S.; R.D.Cumming; N.K. Harpster, D.V.M.; T.E. Moutafis, B.S.; J. Snow, B.S.; C.L.Strohl, B.S.; R. Gardner, B.S.; B. Beaton, B.S.; R.G. Butler, B.S.; F. Petkunas, M.S.; F.E. Sevier, B.S.; M.J. Buckley, M.D.; W.G. Austen, M.D.; P. Block, M.D.; L. Ellman, M.D.; J. Fallon, M.D.; D.M. Philbin, M.D.; W.J. Powell, M.D.; A. Schiller, M.D.

ULTRASOUND B-SCAN ASSESSMENT PROGRAM

Data Coordinating Center for the Ultrasound B-Scan Imaging Assessment Program 91
Fred A. Bryan, Jr., Ph.D.; A. Vijaya Rao, Ph.D.

Ultrasound B-Scan Assessment Program 92
Barry B. Goldberg, M.D.; Stanton N. Smullen, M.D.

DIAGNOSTIC INSTRUMENTATION

Computer Enhancement of Intravenous Coronary Angiograms 95
Robert H. Selzer, M.A., M.S.; David H. Blankenhorn, M.D.; Donald W. Crawford, M.D.

Temporal Filtration Fluoroscopy, Tomography and 3D Display 96
James A. Nelson, M.D.; Robert A. Kruger, Ph.D.; Bruce E. Bray, M.D.; Frederick L. Anderson, M.D.; William H. Barry, M.D.; Brent S. Baxter, Ph.D.

BEST COPY AVAILABLE

Image Processing of Coronary Arteriograms 97
Melvin L. Marcus, M.D.; David J. Skorton, M.D.;
Steve M. Collins, Ph.D.; David G. Harrison, M.D.;
Carl W. White, M.D.; Loren F. Hiratzka, M.D.;
Maryl R. Johnson, M.D.; Elizabeth E. Ericksen, M.S.E.E.;
Steven R. Fleagle, B.S.E.E.; Philip Aylward, M.D.

Visualization of Coronary Arteries and Bypass Grafts 98
Gabor T. Herman, Ph.D.; Leon Axel, M.D., Ph.D.;
Harold Kundel, M.D.; Robert LeVeen, M.D.;
Jayaram K. Udupa, Ph.D.; Gerald Wolf, M.D.

Research, Development and Evaluation of Systems for Noninvasive Detection and Quantification of Atherosclerotic Lesions 99
Ralph W. Barnes, Ph.D.; M. Gene Bond, Ph.D.;
David W. Griffith, Jr., Ph.D.; Ward A. Riley, Jr., Ph.D.

NMR Imaging of Human Coronary Arteries 100
Leon Kaufman, Ph.D.; Lawrence E. Crooks, Ph.D.;
Charles Higgins, M.D.; James Hale, B.A.

Quantification of Coronary Artery Stenosis with the DSR 102
E.L. Ritman, M.D., Ph.D.; R.C. Bahn, M.D., Ph.D.;
A.A. Bove, M.D., Ph.D.; S. Dimolitsas, Ph.D.; L.D. Harris, Ph.D.;
P.B. Heffernan, Ph.D.; R.A. Robb, Ph.D.; H.C. Smith, M.D.

K-Edge Subtraction Angiography with Synchrotron X-Rays 103
R. Hofstadter, Ph.D.; E.B. Hughes, Ph.D.; E. Rubenstein, M.D.;
H.D. Zeman, Ph.D.; M. Buchbinder, M.D.; D.C. Harrison, M.D.;
A.C. Thompson, Ph.D.; G.S. Brown, Ph.D.

Development and Evaluation of Minimally Invasive Systems for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries in Humans 104
Donald Sashin, Ph.D.; Klaus M. Bron, M.D.

Research, Development, and Evaluation of Minimally Invasive Systems for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries of Humans 105
Theron W. Ovitt, M.D.; Hans Roehrig, Ph.D.

Research, Development and Evaluation of Systems for Noninvasive Detection and Quantification of Atherosclerotic Lesions in Peripheral and Coronary Arteries in Humans 106
Charles A. Mistretta, Ph.D.

Visualization and Quantitation of Coronary Arteries Using Multiple-View Energy Subtraction Digital Radiography 107
Albert Macovski, Ph.D.

The DSR, Status Report '84 108
Erik L. Ritman, M.D., Ph.D.; Douglas D. Mair, M.D.;
Joseph R. Rodarte, M.D.; Kai Rehder, M.D.;
Richard A. Robb, Ph.D.; Lowell D. Harris, Ph.D.

BEST COPY AVAILABLE

Ultrasonic Instrumentation for Cardiovascular Studies 109
Craig J. Hartley, Ph.D.; Robert M. Lewis; Mark L. Entman, M.D.; George P. Noon, M.D.; Robert M. Nerem, Ph.D.; Lloyd H. Michael, Ph.D.

Hemodynamics of Normal and Diseased Carotid Arteries 110
Don P. Giddens, Ph.D.; Richard I. Kitney, Ph.D.

Noninvasive Assessment of Pediatric Atherosclerosis 111
Ward A. Riley, Jr., Ph.D.; David Freedman, Ph.D.; Gerald Berenson, M.D.; Ralph W. Barnes, Ph.D.

Assessment of In Vivo Passive Myocardial Stiffness 112
Krishnan B. Chandran, D.Sc.; David J. Skorton, M.D.; Steve Collins, Ph.D.; Richard Kerber, M.D.; Melvin Marcus, M.D.

Noninvasive Cerebral Blood Flow Measurement 113
Joseph H. Battocletti, Ph.D.; Anthony Sances, Jr., Ph.D.

Local Cerebral Blood Flow by Serial CT Imaging 114
David Gur; Sidney K. Wolfson, Jr.; Howard Yonas; David L. Jackson; Walter F. Good; Richard E. Latchaw; William H. Kennedy; Eugene E. Cook; Barbara C. Good

Dynamic Radiographic Assessment of Myocardial Function 115
Joseph J. McInerney, Ph.D.; Edward S. Kenney, Ph.D.; Robert F. Zelis, M.D.

Development and Testing of Clinical Blood Viscometer 116
Mitchell Litt, D.Eng.Sc.; John Seybert

Computer Technology for Transaxial Tomography 117
Gabor T. Herman, Ph.D.; Robert M. Lewitt, Ph.D.; Nathaniel Reichek, M.D.; Sushma S. Trivedi, Ph.D.

Ultrasonic Scattering by Biological Tissues 118
K. Kirk Shung, Ph.D.; Terry M. Wilson, D.V.M.; John Tarbell, Ph.D.

Automatic Processing of Digital Echocardiography 119
Andrew J. Buda, M.D.; Edward J. Delp, Ph.D.; Charles R. Meyer, Ph.D.; Fred L. Bookstein, Ph.D.

Tomographic Digital Subtraction Angiography 120
Robert A. Kruger, Ph.D.; James A. Sorenson, Ph.D.; James A. Nelson, M.D.

BEST COPY AVAILABLE

THERAPEUTIC INSTRUMENTATION AND DEVICES

Elimination of Reoperative Cardiac Pacemaker Surgery 123
Howard C. Hughes, V.M.D., M.S.

Waveform Dependency in Defibrillation 124
John C. Schuder, Ph.D.; Harry Stoeckle, M.D.;
Wayne C. McDaniel, M.S.E.E.

Thermal Control of Heart Rate 125
Victor Parsonnet, M.D.; David Glass, M.D.;
Alexander Villanueva, B.Sc.

Defibrillator Waveshape Optimization 126
Janice L. Jones, Ph.D.; Ronald E. Jones, M.S.E.E.

Defibrillator Induced Dysfunction 127
Janice L. Jones, Ph.D.; Ronald E. Jones, M.S.E.E.

Swallowable Electrodes for Temporary Cardiac Pacing 128
Janice M. Jenkins, Ph.D.; Robert Arzbaecher, Ph.D.;
Charles Yurkonis, M.S.

BEST COPY AVAILABLE

BLANK PAGE

STAFF

DEVICES AND TECHNOLOGY BRANCH
DIVISION OF HEART AND VASCULAR DISEASES
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Federal Building, Room 312
7550 Wisconsin Avenue
Bethesda, Maryland 20205
Telephone: 301-496-1586

Branch Chief: John T. Watson, Ph.D.

Deputy Chief: Frank D. Altieri, Ph.D.

Senior Staff Scientists: Alan S. Berson, Ph.D.

Rosalie A. Dunn, Ph.D.

Suzanne G. Eskin, Ph.D.

Secretarial Staff: Marjorie S. Suttora

Agnes G. Hardy

Janet L. Krasnican

Sally Swanson

BEST COPY AVAILABLE

BLANK PAGE

Meeting Schedule Overview

BEST COPY AVAILABLE

BLANK PAGE

AGENDA

1984 DEVICES AND TECHNOLOGY BRANCH CONTRACTORS MEETING
DECEMBER 5-7, 1984
HOLIDAY INN CROWNE PLAZA HOTEL, ROCKVILLE, MARYLAND

Tuesday, December 4, 1984

6:00 - 9:00 p.m.	Registration Desk Open	Randolph Room
6:00 - 8:00 p.m.	Social Hour	Upper Pavillion

****

POSTERS AND DISPLAYS

Ventricular Assist Systems on display in the Regency Room, Wednesday and Thursday.

Primary Reference Materials on display in the Regency Room, Wednesday.

****

THE HASTINGS LECTURE WILL BE PRESENTED AT 10:00 A.M., THURSDAY

****

Wednesday, December 5, 1984

7:15 a.m.	Registration	Randolph Room
	PLENARY SESSION	Plaza II and III
7:45 a.m.	Devices and Technology Branch Program Overview **Dr. John T. Watson**	
8:00 a.m.	NHLBI Research Training and Development **Dr. Donald MacCanon**	

BEST COPY AVAILABLE

BIOMATERIALS SESSION — Plaza II and III

Chairpersons: **Dr. Sumner Barenberg**
Dr. John Sharefkin

Calcification of Prosthetic Materials Program

8:15 a.m. — Prosthetic Materials in the Cardiovascular System
Dr. Walter E. Brown

8:30 a.m. — Calcification Mechanisms in Cardiovascular Prostheses
Dr. James W. Buchanan

8:45 a.m. — Quantification of Regional Platelet Thrombosis and Regional Calcium Mapping on Pericardial Tissue Valve Prostheses with Diphosphonate Treatment
Dr. Mrinal K. Dewanjee

9:00 a.m. — Structural Proteins in Bioprosthetic Valve Calcification
Dr. Robert J. Levy

9:15 a.m. — Mechanical Etiology of Calcification
Dr. Param Singh

9:30 a.m. — Considerations in Deposition and Degradation of Calcified Deposits in Cardiac Assist Devices
Dr. Jane Lian

9:45 - 10:15 a.m. — Coffee Break — Regency Room

10:15 - 10:45 a.m. — Guest Speaker: **Dr. H. Clarke Anderson**
Chairman, Department of Pathology
University of Kansas
"Role of Membranes in Skeletal Calcification"

Small Diameter Vascular Grafts Program

10:45 a.m. — Endothelial Seeding of Small Vessel Prostheses
Dr. Allan D. Callow

11:00 a.m. — Endothelial Seeding of Vascular Grafts
Dr. John Glover and Dr. Malcolm Herring

11:15 a.m. — Effects of Compliance Mismatch in Arterial Grafts
Dr. William A. Abbott

11:30 a.m. — Application of Arterial Regeneration
Dr. Howard P. Greisler

11:45 a.m. — Endothelialization of Detergent-Extracted Canine Vascular Matrix
Dr. Klaus Brendel and Dr. Raymond C. Duhamel

BEST COPY AVAILABLE

Wednesday, December 5, 1984 (Continued)

12:15 p.m.	LUNCHEON Guest Speaker: **Ms. Karen Ramberg** Assistant Professor of Radiology Tufts University Medical School "Where Are the Platelets?"	Plaza I
	*BIOMATERIALS SESSION (Continued)	Plaza II and III
2:30 p.m.	Graft Thrombus Formation and Therapeutic Thrombolysis **Dr. Stephen R. Hanson**	Plaza II and III
2:45 p.m.	Bioresorbable Vascular Grafts **Dr. Pierre M. Galletti**	Plaza II and III
3:00 p.m.	Surface Structure and Surface Biological Interactions of Polyether Urethanes **Dr. Buddy D. Ratner**	Plaza II and III
3:15 p.m.	Chairpersons' Summaries	Plaza II and III
	*ENERGY TRANSMISSION SYSTEMS SESSION	Conference Theater
	Chairpersons: **Dr. Edwin Alderman** **Dr. Lee Baker** **Dr. Hynda Kleinman**	
2:30 p.m.	Research and Development of Systems for Transmitting Energy Through Intact Skin **Mr. Craig Sherman**	Conference Theater
2:45 p.m.	Electrical Energy Transmission through Intact Skin **Dr. Peer Portner**	Conference Theater
3:00 p.m.	Development of a Percutaneous Energy Transmission System **Dr. Adrian Kantrowitz**	Conference Theater
3:15 p.m.	Development of a Percutaneous Energy Transmission System **Dr. Benedict Daly**	Conference Theater
3:30 - 4:00 p.m.	Coffee/Cookie Break	Regency Room

*NOTE: THESE ARE SIMULTANEOUS SESSIONS

BEST COPY AVAILABLE

Wednesday, December 5, 1984 (Continued)

	Biomaterials/Reference Materials Program	Conference Theater
4:00 p.m.	Panel on NHLBI Reference Materials Moderator: **Dr. Suzanne G. Eskin**	
	The Biocompatibility of NHLBI Reference Materials **Dr. James M. Anderson**	
	Panel Members: **Dr. Robert I. Leininger** **Dr. Sumner Barenberg** **Dr. Buddy D. Ratner** **Dr. Paul Didisheim**	
5:15 p.m.	Adjourn	
6:00 - 8:00 p.m.	Social Hour	Upper Pavillion

Thursday, December 6, 1984

	MECHANICAL CIRCULATORY SUPPORT SESSION	Plaza II and III
	Chairpersons: **Dr. Edwin Alderman** **Dr. Lee Baker** **Dr. Hynda Kleinman**	
	Thermal Energy Ventricular Assist Systems Program	
8:30 a.m.	Development of a Thermal Ventricular Assist System **Mr. Maurice White**	
8:50 a.m.	Development and Evaluation of a Thermocompressor Powered Thermal Energy System **Dr. John Moise**	
9:10 a.m.	Small Business Innovation Research (SBIR) Program	
	Ms. Lily Engstrom SBIR Program Coordinator, NIH	
9:40 - 10:00 a.m.	Coffee Break	Regency Room
10:00 a.m.	HASTINGS LECTURE **Dr. John C. Norman** Cardiac Surgery Beth Israel Medical Center "The Hastings File: A Search for Solutions"	Plaza II and III

BEST COPY AVAILABLE

Thursday, December 6, 1984 (Continued)

	Electrical Energy Ventricular Assist Systems Program	Plaza II and III
11:00 a.m.	Development of an Implantable, Integrated Electrically-Actuated Left Heart Assist System **Dr. O. Howard Frazier**	
11:20 a.m.	Development of an Implantable Integrated Electrically-Powered Left Heart Assist System **Dr. David Gernes**	
11:40 a.m.	Electrohydraulic Left Heart Assist System **Dr. Param Singh**	
12:15 p.m.	LUNCHEON Guest Speaker: **Dr. Larry W. Stephenson** Associate Professor of Surgery School of Medicine, University of Pennsylvania "Myocardial Augmentation Using Skeletal Muscle"	Plaza I
	Electrical Energy Ventricular Assist Systems Program (Continued)	Plaza II and III
2:00 p.m.	Development of an Electrohydraulic Driven Left Heart Assist System **Dr. John Moise**	
2:20 p.m.	Development of an Implantable Left Heart Assist System **Dr. Peer Portner**	
2:40 - 2:50 p.m.	DISCUSSION	
2:50 - 4:00 p.m.	PANEL: PHYSIOLOGY AND PATHOPHYSIOLOGY OF CIRCULATORY SUPPORT DEVICES Moderator: **Dr. John Watson** Panelists: To be Announced	
4:00 - 4:15 p.m.	Coffee/Cookie Break	Regency Room

BEST COPY AVAILABLE

Thursday, December 6, 1984 (Continued)

4:15 - 4:45 p.m.	PANEL: DEVICE READINESS TESTING OF ELECTRICALLY POWERED VAS	Plaza II and III
	Moderator: **Dr. Frank Altieri**	
	Panel Members: **Mr. Warren Clay** **Dr. John Moise** **Dr. Peer Portner** **Dr. Param Singh**	
4:45 p.m.	Chairpersons' Summaries of VAS and Energy Transmission Sessions	
5:15 p.m.	Adjourn	
6:00 - 8:00 p.m.	Social Hour	Upper Pavillion

Friday, December 7, 1984

	DIAGNOSTIC INSTRUMENTATION SESSION	Plaza II and III
8:15 a.m.	Devices and Technology Branch Program Overview **Dr. John T. Watson**	
8:30 - 10:00 a.m.	Ultrasound B-Scan Assessment Program	
	Moderator: **Dr. Alan Berson**	
	Panel Members: **Dr. James Toole**, Chairman **Dr. Gene Bond** **Dr. Fred Bryan** **Dr. Barry Goldberg** **Dr. Daniel O'Leary** **Dr. Jeff Raines** **Dr. John Ricotta**	
	Presentations: **Drs. Raines, Ricotta, O'Leary, and Bond**	
10:00 - 10:30 a.m.	Coffee Break	Plaza Foyer

BEST COPY AVAILABLE

Image Enhancement of Coronary Arteries Program — Plaza II and III

Chairpersons: **Dr. James Bailey**
Dr. Robert Kruger
Dr. John Reid

10:30 a.m. Computer Enhancement of Intravenous Coronary Angiograms
Mr. Robert Selzer

10:45 a.m. Temporal Filtration Fluoroscopy/Tomography/3-D
Dr. James Nelson

11:00 a.m. Image Processing of Coronary Arteriograms
Dr. Melvin Marcus

11:15 a.m. Visualization of Coronary Arteries and Bypass Grafts
Dr. Gabor Herman

Detection and Quantification of Lesions in Deep-Lying Arteries and in Coronary Arteries Program

Chairpersons: **Dr. James Bailey**
Dr. Robert Kruger
Dr. John Reid

11:30 a.m. Ultrasound System for Detection and Quantification of Lesions in Animals
Dr. Ralph Barnes

11:45 p.m. Noninvasive Detection and Quantification of Atherosclerotic Lesions--NMR Methods
Dr. Leon Kaufman

12 noon LUNCHEON — Plaza I
Guest Speaker: **Dr. William Long**
Research Associate
Laboratory for Computer Science
Massachusetts Institute of Technology
"Artificial Intelligence Techniques Applied to the Cardiovascular System"

BEST COPY AVAILABLE

	Detection and Quantification of Lesions in Deep-Lying Arteries and in Coronary Arteries Program (Continued)	Plaza II and III
1:30 p.m.	Digital Coronary Angiography **Dr. Martin Kaplitt**	
1:45 p.m.	Minimally Invasive System for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries **Dr. Robert Hofstadter** **Dr. Barrie Hughes**	
2:00 p.m.	Minimally Invasive System for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries **Dr. Erik Ritman**	
2:15 p.m.	Minimally Invasive System for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries **Dr. Donald Sashin**	
2:30 p.m.	Minimally Invasive System for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries **Dr. Theron Ovitt**	
2:45 p.m.	Minimally Invasive System for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries **Dr. Charles Mistretta**	
3:00 p.m.	Minimally Invasive System for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries **Dr. William Brody**	
3:15 p.m.	Chairpersons' Summaries	
3:30 p.m.	Closing Remarks **Dr. John T. Watson**	
	Adjourn	

BEST COPY AVAILABLE

Calcification of Prosthetic Materials

BEST COPY AVAILABLE

BLANK PAGE

AMERICAN DENTAL ASSOCIATION HEALTH FOUNDATION
Prosthetic Materials in the Cardiovascular System
GRANT NUMBER: 5 R01 HL 30035-02

A serious need exists for a better understanding of the thermodynamic, kinetic, and structural factors governing a wide variety of biological calcifications, including those that occur in the arterio-venous system. We have made significant progress in all three of these areas. Equilibration techniques, originally developed for pure calcium phosphate systems, were applied to ultrafiltered serum and to the mineral in arteriosclerotic plaque. After equilibration of serum with $CaHPO_4 \cdot 2H_2O$ (DCPD), $Ca_8H_2(PO_4)_6 \cdot 5\ H_2O$ (OCP), or $Ca_5(PO_4)_3OH$ (OHAp), Ca and PO_4 concentrations and pH were measured, and the results were used to calculate the degrees of saturation of serum with respect to the above solids.

Results: (1) Native, ultrafiltered serum was found to be approximately saturated with respect to OCP, highly undersaturated with respect to DCPD, and highly supersaturated with respect to OHAp. Thus, OCP appears to establish the level of saturation of serum. (2) Ultrafiltered serum was found to be essentially free of ions that complex Ca and PO_4. (3) After prolonged equilibration of serum with DCPD, the level of saturation decreased to that of OCP and X-ray diffraction of the solid phase revealed that it had transformed to OCP. After further equilibration the solution composition approached saturation with respect to OHAp. This proves that the transformation sequence, DCPD → OCP → OHAp, can take place in serum. (4) The above results, if confirmed by additional studies, establish the feasibility of OCP as a precursor in the formation of mineral on prosthetic devices, in atherosclerotic plaque, and in other passive pathological calcifications. (5) Lipid-extracted, enzyme-treated plaque repeatedly equilibrated with acid revealed an apparent solubility equivalent to that of β-$Ca_3(PO_4)_2$. (6) The experimental techniques we have developed and the concepts we have derived from the results have application for the study of a wide range of pathological calcifications.

Walter E. Brown, Ph.D., Principal Investigator
Laurence C. Chow, Ph.D., Co-Investigator
Branko Tomazic, Ph.D., Co-Investigator
Naomi Eidelman, Ph.D., Research Associate

BEST COPY AVAILABLE

UNIVERSITY OF PENNSYLVANIA
Calcification Mechanisms in Cardiovascular Prostheses
GRANT NUMBER 5 R01 HL 29979-03

Calcification of bioprosthetic heart valves and artificial heart or assist device bladders continues to limit progress in these fields. Our studies of calcification mechanisms include in vivo and in vitro methods. Cardiac patch grafts of glutaraldehyde-fixed bovine pericardium (Pc) were mounted on rigid epoxy rings and implanted as myocardial windows in the right atrium and right ventricle of young sheep. Excess portions of Pc obtained in trimming the implants were placed subcutaneously. Time course studies have demonstrated focal or diffuse thrombosis at one to 2 weeks but little or no thrombus in specimens left in for 4 weeks. After 2 weeks mineral was often evident in low energy soft tissue radiographs at necropsy but absent in antimortem fluoroscopy, radiographs and computed axial tomography. Pc grafts processed and supplied in a phosphate buffered system appeared to have more calcification than those processed in an acetate buffer. Light microscopy and scanning electron microscopy with EDX show evidence of layering of mineral within the pericardium and also within the organizing thrombus that forms a pseudoneointima (PNI) on the blood contacting surface.

In biochemical studies, Pc explants were analyzed for inorganic Ca and P, alkaline phosphatase activity, total protein and lipid phosphorus. When considered as a function of implant time, it was found that the heterograft calcifies, and that the calcification is time-dependant although, in all samples analyzed, the pattern of calcification was irregular. Alkaline phosphatase activity in the explants was similar to that of serum for short implantations, and then declined to about 10 percent of the initial value by 120 days of implantation. While deposits of phospholipids and proteins were detected, a mechanistic relationship between deposition of these materials and calcification could not be established.

In in vitro experiments, Pc patches were exposed to pulsatile stress in the presence of normal saline or sheep serum. Control patches were exposed to serum in a passive manner. Mineralization was scored using an analytical scheme similar to that used for the in vivo samples. The results of these experiments show that both stressed and passive exposure of the pericardium to serum could lead to the accumulation of ions, lipids and proteins. The rate of accumulation was slow, with most components reaching maximum values in 1-3 hours. In some experiments, pumping stresses resulted in enhanced uptake of mineral ions. Comparison of the proteins extracted from calcified explants with normal sheep serum revealed no pattern of selective protein adsorption.

James W. Buchanan, D.V.M., M.Sc., Principal Investigator
Julius Melbin, V.M.D., Ph.D., Investigator-Hemodynamics
Irving M. Shapiro, B.D.S., Ph.D., Investigator-Biochemistry
Ellis E. Golub, Ph.D., Investigator-Biochemistry
Jeffrey M. Dunn, M.D., Investigator-Surgery
Peter Frasca, Ph.D., Investigator-Ultrastructure

BEST COPY AVAILABLE

MAYO CLINIC AND MAYO FOUNDATION
Quantification of Regional Platelet Thrombosis and Regional Calcium Mapping on Pericardial Tissue Valve Prosthesis with Diphosphonate Treatment in Calves
Grant Number HL-28974

Ninety-five Holstein calves were implanted with 25 mm Ionescu-Shiley pericardial tissue valve prostheses in mitral annulus and two 2 cm x 2 cm glutaraldehyde-fixed pericardial patches under the skin in the abdomen. Calves in the control and diphosphonate (DP) treated groups were killed at 1, 14, 30 and 90 days post valve prosthesis implantation. In the treated group diphosphonate solution was administered subcutaneously. Platelet thrombosis in the components of tissue valve was noninvasively imaged with autologous ^{111}Indium-labeled platelets, and after harvesting the valve and dissections, regional platelet thrombosis was quantified with ^{111}In-labeled platelets. Twenty-four hours before killing 700-800 microcuries of ^{45}Calcium chloride and 500-700 microcuries of autologous ^{111}In-labeled platelets were administered intravenously. Platelet and fibrinogen consumption was further quantified by platelet survival with ^{111}In-platelets and ^{125}I-labeled bovine fibrinogen, respectively, at seven days preoperation, immediately postoperation, 14 and 45 days post-implantation.

After explantation each leaflet was carefully separated from the sewing ring and mapped for regional platelet thrombosis and calcification. Total calcium in four zones of leaflets (Fig. 1) and sewing ring was determined by atomic absorption spectrometry and further checked by energy dispersive x-ray analysis (Ca, P). Endothelial cell coverage of leaflets was monitored by scanning electron microscopic technique. Results of regional calcification in the control and DP-treated calves at 1, 14, 30 and 90 days post-implantation are shown in Table I.

Although the results indicate that DP treatment reduces calcification, in all sections of leaflets at 90 days the side effect (inhibition of bone growth) is severe enough to prevent its clinical trial. We have recently developed a new technique of processing collagenous tissue. This involves removal of antigenic proteins with detergents, immobilization of immunosuppressive drugs, including diphosphonate derivatives, stabilization of drug-collagen bond by borohydride reduction and removal of excess glutaraldehyde before implantation. This processing of pericardial tissue promotes spontaneous endothelial cell coverage of entire leaflet surface. Our preliminary granulocyte retention study with ^{111}In-labeled granulocyte on leaflet surface also indicates that granulocyte infiltration is reduced due to this processing technique. This suggests that removal of antigenic sites and immobilization of immunosuppressive drug reduce leukocyte infiltration, which is known to inhibit endothelial cell coverage of cardiovascular prostheses.

Mrinal K. Dewanjee, Ph.D., Principal Investigator
Michael P. Kaye, M.D., Coinvestigator (Surgical Research)
William D. Edwards, M.D., Coinvestigator (Cardiac Pathology)
Paul Didisheim, M.D., Coinvestigator (Hematology Research)
James H. Chesebro, M.D., Consultant (Cardiac Research)
Paul H. Wooley, Ph.D., Consultant (Immunology Research)
Steven S. Barham, Ph.D., Consultant (Cell Biology)
Paul E. Zollman, Consultant (Veterinary Medicine)

BEST COPY AVAILABLE

Table I Time Course of Increase in Calcification by Regional Mapping of Calcium (μg/mg of wet tissue) in Leaflets of Control and Diphosphonate-Treated Calves Implanted with 25 mm Pericardial Tissue Valves.

CONTROL CALVES

	1 Day (n=8)	14 Days (n=5)	30 Days (n=6)	90 Days (n=6)
Free Edge	0.11 ± 0.04	0.49 ± 0.57	2.63 ± 3.42	30.54 ± 29.99
Central Zone	0.11 ± 0.20	0.45 ± 0.43	1.38 ± 2.57	23.51 ± 14.17
Flexion Zone	0.16 ± 0.40	2.06 ± 1.96	3.34 ± 3.23	36.76 ± 20.22
Attachment Zone	0.13 ± 0.06	2.85 ± 2.55	10.73 ± 12.57	33.55 ± 20.19
Sewing Ring	0.74 ± 0.77	0.72 ± 0.42	0.68 ± 0.39	0.62 ± 0.37

DIPHOSPHONATE-TREATED CALVES

	1 Day (n=6)	14 Days (n=6)	30 Days (n=8)	90 Days (n=6)
Free Edge	0.15 ± 0.04	0.82 ± 0.42	7.33 ± 6.26	8.94 ± 14.51
Central Zone	0.14 ± 0.02	0.75 ± 0.50	4.53 ± 3.28	5.90 ± 7.24
Flexion Zone	0.23 ± 0.26	0.92 ± 0.56	2.95 ± 4.01	16.53 ± 21.20
Attachment Zone	0.11 ± 0.04	0.38 ± 0.35	1.43 ± 1.59	1.35 ± 1.69
Sewing Ring	0.17 ± 0.06	0.40 ± 0.31	0.35 ± 0.25	0.27 ± 0.19

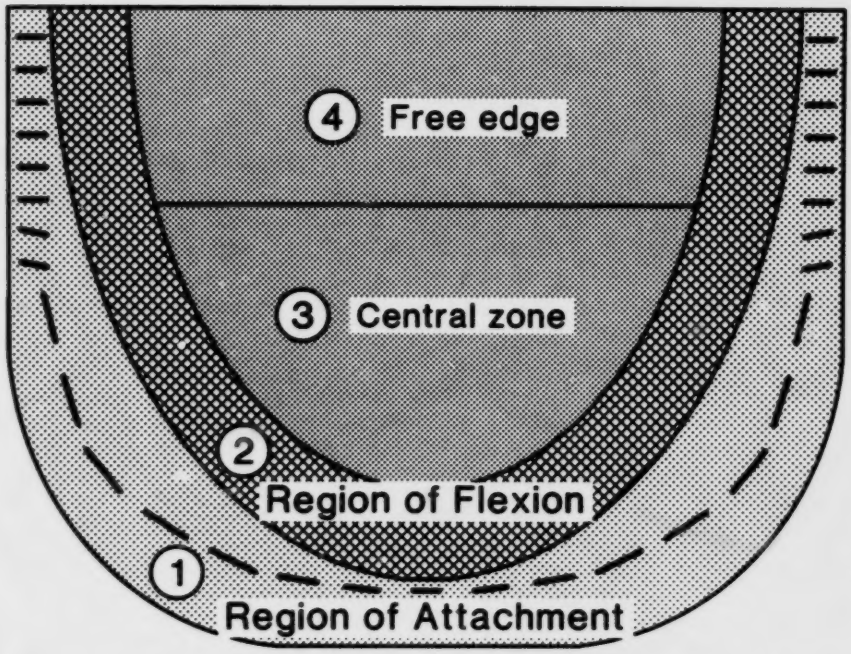
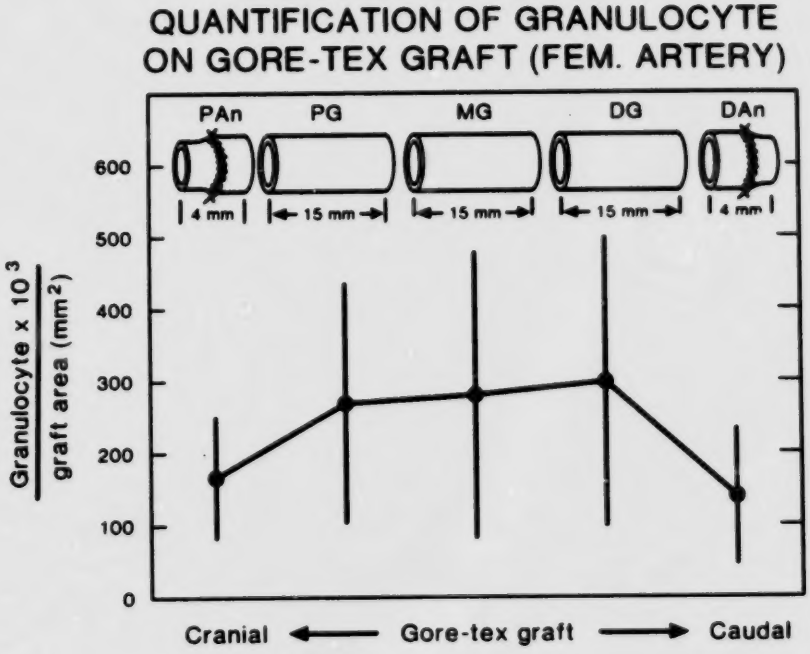


Figure 1. The four zones for mapping of calcification and thrombosis in each leaflet of tissue valve prosthesis implanted in calves.

BEST COPY AVAILABLE

MAYO CLINIC AND MAYO FOUNDATION
Quantification of Granulocyte Deposition on Vascular Grafts in Dogs with ^{111}In-Labeled Granulocytes
Grant Number HL-28974

A new radioisotopic technique has been developed for quantification of granulocyte deposition on vascular grafts. Nine healthy mongrel dogs underwent bilateral femoral implants with grafts of femoral vein and 4 mm Gore-Tex grafts. Pure granulocytes separated from whole blood by centrifugal elutriation technique were labeled with ^{111}In-tropolone in plasma. Granulocyte harvesting efficiency was (25 ± 12)% and labeling efficiency was (87 ± 7)%. Three hours post-injection of labeled granulocytes (282 ± 115) x 10^6 and two hours post-reperfusion the grafts were harvested and cut into several segments to study areas of anastomoses and midsections of grafts. From the radioactivity in blood and graft sections, area of graft sections, anastomoses and granulocyte counts and differential white cell counts, number of granulocytes adherent to unit area of graft sections were calculated. These quantifications of granulocyte deposition indjcate that midsections of Teflon graft retain more granulocytes (260 x 10^3/mm^2) than midsections of vein grafts (20 x 10^3/mm^2). Anastomoses of vein grafts retain more granulocytes (40 x 10^3/mm^2) than midsections and vice versa for the Gore-Tex grafts. A major fraction of granulocytes on Gore-Tex grafts are incorporated into thrombus. Semiquantitative information obtained by scintigraphy of granulocyte deposition on vascular graft with computerized gamma camera also confirms this observation. This technique thus permits us to study granulocyte deposition on vascular grafts and the effect of granulocytes on inhibition of endothelial cell coverage of cardiovascular prostheses.



Mrinal K. Dewanjee, Ph.D., Principal Investigator
Michael P. Kaye, M.D., Coinvestigator (Surgical Research)

BEST COPY AVAILABLE

THE CHILDREN'S HOSPITAL, BOSTON, MASSACHUSETTS
Structural Proteins in Bioprosthetic Valve Calcification
GRANT NUMBER: 5 R01 HL32346-02

Collagen calcification is an important feature of the pathologic mineralization of bioprosthetic heart valves. In the second year of this program research has focused on the following: (1.) The events which precede and lead to collagen calcification in bioprosthetic heart valve calcification; (2.) The fate of implants of purified Type I collagen; and (3.) the importance to calcification of residual aldehyde functions after glutaraldehyde pretreatment of collagenous implants.

Studies of the early events in bioprosthetic cusp subcutaneous implants (both bovine pericardial and porcine aortic) indicate that initial calcific deposits first appearing after 48 hours of implantation are predominantly associated with devitalized cell membrane structures. After 14 days, in both types of implants, collagen calcification and membrane oriented deposits become equally prominent, eventually forming calcific nodules which destroy the cuspal integrity. The kinetics of both pericardial and porcine bioprosthetic implant calcification appear to be identical and plateau at peak levels after 60 days of subcutaneous implantation.

Subcutaneous implants of purified Type I collagen, the principal collagen present in bioprosthetic cusps, calcify only if they are pretreated with aldehyde based cross-linking reagents, either glutaraldehyde or formaldehyde (Table I). Non-treated collagen implants were completely resorbed without calcifying. It is of interest that the extent of calcification did not appear to be related to the duration of exposure to the cross-linking agents, or the degree of cross-linking as determined by shrinkage temperature and collagenase digestibility. Studies of the importance to calcification of residual aldehyde groups remaining after glutaraldehyde pretreatment of collagen examined the covalent incorporation of aminohydroxydiphosphonate (APDP). It was hypothesized that residual aldehyde groups would form Schiff-base compounds with the amino function of APDP, and that this bound diphosphonate might inhibit the events of collagen calcification. APDP pretreatment (0.14M APDP, pH 7.4 for 24 hours) significantly inhibited collagen calcification (Table I) compared to control. Similar results were obtained pretreating porcine aortic cusps with APDP. Future work in this program will further investigate the importance of the collagen-glutaraldehyde interaction, the effects of bound pharmacologic agents, such as APDP, and the relationships during early crystal formation between collagen and other matrix components involved in the calcification process.

TABLE I

Calcification of Glutaraldehyde Pretreated Collagen Implants

Experiment	N	Ca++(ug/mg)
Glutaraldehyde (Glut.) pretreated	14	56.5±6.3
Formaldehyde Pretreated	14	98.6±5.4
Glut.Plus APDP*	10	1.8±0.2
Porcine Aortic Cusp (PAC)	19	154.9±4.1
PAC Plus APDP	10	24.2±7.4

Robert J. Levy, M.D., Principal Investigator
Frederick J. Schoen, M.D., Ph.D., Pathologist (Brigham and Women's Hospital)
Alan C. Nelson, Ph.D., Biophysicist (Massachusetts Institute of Technology)

BEST COPY AVAILABLE

ABIOMED (Applied Biomedical Corporation)
MECHANICAL ETIOLOGY OF CALCIFICATION
1-R01-HL-30013

There is evidence in the literature to strongly suggest a correlation between mechanical factors and intrinsic dystrophic calcification on prosthetic blood contacting surfaces. The purpose of this study is to elucidate this connection using the calf as an accelerated model. Experiments involve fabrication, characterization, implantation, retrieval, and subsequent analyses of valved conduits whose surface morphology can be systematically varied and where the spatial distributions and quantitative levels of mechanical strain and fluid dynamic shearing stresses are known.

During the past year, there were ten implants of left ventricle to aorta valved conduits (with ligation of the ascending aorta). Three were early surgical failures due primarily to inflow cannula misalignment. The remaining seven were terminated electively at gradually increasing implant durations of 27, 73, 106, 120, and 154 (three experiments) days. No anticoagulant or antithrombotic pharmacologic therapy was used. Except for the 120 day implant, the conduit surfaces and trileaflet valves were fabricated from smooth Angioflex® polyurethane. The 120 day implant was identical except that a section of conduit distal to the trileaflet valve had a textured Angioflex® surface. The valve leaflet thickness resulted in 8-10% mechanical strain at the leaflet conduit junction.

Mean conduit flow ranged from 6-8 liters/minute at implantation to 11-15 liters/minute at termination of the longer implants. Thus, transient peak fluid dynamic shear stresses on the conduit surfaces distal to the trileaflet valve ranged from 800 dynes/cm^2 at implant to approximately 2000 dynes/cm^2 at explant after 22 weeks. Peak fluid dynamic stresses on conduit surfaces proximal to the trileaflet valve ranged from 50 to 125 dynes/cm^2 .

Hematological parameters were within normal limits for the calf model. Preoperative osteocalcin levels were much higher than adult human values (6-10 ng/dl). There were wide variations between different animals with values ranging from 25 ng/ml to 250 ng/ml. This variation may partially explain why wide variations in calcific deposits have been observed using this model.

Conduits explanted after 27, 73, and 106 days were devoid of calcification (examined by SEM/EDAX). Conduits explanted after 120 and 154 days (three experiments) all showed calcification easily discerned by SEM/EDAX. The peak osteocalcin levels in the conduits with calcific deposits ranged from 138 to 187 ng/ml. The peak level for the 106 day non-calcified implant was 246 ng/ml.

BEST COPY AVAILABLE

Observations on the nature and distribution of calcific deposits can, at this time, be summarized as follows:

1. Two kinds of deposits have been observed on smooth surfaces:

   (a) Gross, rough, "heavier" deposits that are found on moving surfaces and appear to correlate with areas of mechanical strain. Some of these deposits could be visually observed.

   (b) Flat plate like "plaque" deposits are found on both moving and non-moving surfaces. These deposits had very regular distinct shapes with very flat profiles ($< 2\mu m$ in height) and could be only observed by SEM. In some areas, these plaques grow to cover the surface with a flat layer.

2. The "plaque" deposits appear to be a surface phenomenon. They were not found in large surface defects ($> 5\text{-}10\mu m$). However, there may be a correlation with submicron scale surface morphology. They also appear to be precursors for the "heavier" deposits.

3. At this time, we do not have a quantitive measure of the amount of deposits and their correlation fluid shear stresses, but qualitatively calcification appears heavier at areas of higher stresses.

4. The one experiment (120 days) with a textured conduit showed the "heavier" kind of calcification, but only at the blood contacting surface layer.

The major questions to be addressed by future work is the nature and genesis of the flat "plaque" deposits.

Param I. Singh, Ph.D., Principal Investigator
Robert D. Cumming, Senior Investigator
Jeffrey L. Snow, B.S., Senior Investigator
Loyde H. Romero, M.D., Ph.D., Co-Investigator
Neil K. Harpster, D.V.M., Co-Investigator (Angell Memorial Hospital)
Jane B. Lian, Ph.D., Co-Investigator
(Children's Hospital Medical Center)

BEST COPY AVAILABLE

THE CHILDREN'S HOSPITAL, HARVARD MEDICAL SCHOOL
Blood-Material Interactions: Calcification
GRANT NUMBER: HL32356

Considerations in Deposition and Degradation of Calcified Deposits in Cardiac Assist Devices

Microscopic observations of calcific deposits formed on textured Biomer surfaces of left ventricular assist devices that develop a pseudointimal (PI) matrix have revealed the following associations. Calcification is initiated at the polymer-PI junction and in discontinuous areas of the matrix due to poor adherence of the PI. The calcific deposits are hydroxyapatite and are prevalent on the flexing axes of the blood pump or any area of strain or decreased blood flow. Specific sites of calcification which have been identified include bacteria, plasma membrane of degenerated cells, intracellular vesicles of macrophages, nuclei of giant cells which predominate on Dacron flocked fibril surfaces but not Biomer fibrils.

Our studies have focused on the identification and role of specific calcium-binding proteins associated with the calcific deposits in order to understand fundamental mechanisms of mineral accretion in pathologic calcifications. We have identified serum proteins rich in plaques that are also accumulated in bone, albumin, α2glycoprotein, O-phosphoserine containing proteins and osteocalcin. A linear correlation of the vitamin K dependent bone, osteocalcin, with calcium occurs in a variety of pathologic calcifications (inflammatory subcutaneous calcification, heart valves, kidney stones) and including the blood pumps from anticoagulated cows. Although sodium warfarin inhibits synthesis of the γ-carboxyglutamic acid residues which promote calcium binding, the protein is rich in glutamic and aspartic acid and still has hydroxyapatite binding potential. Certain physiologic circumstances dictate high circulating levels of the bone protein, such as in healthy rapidly growing young animals and children and during sodium warfarin treatment.

Although osteocalcin is synthesized in concert with new bone formation and mineralization, we have just identified that its precise function is in the regulation of bone resorption. Synthesis is stimulated by $1,25(OH)_2D_3$ and bone that is deficient in osteocalcin is poorly resorbed in both *in vivo* and *in vitro* models. Osteocalcin and α2glycoprotein have chemoattractant activity for monocytes and macrophages and can stimulate phagocytosis. Thus we now have an appreciation for a potentially beneficial role for certain proteins with affinity for hydroxyapatite. We are currently using these models to test the degradation of calcific deposits from cardiac assist devices and other pathologic deposits.

Jane B. Lian, Ph.D., Principal Investigator

BEST COPY AVAILABLE

BLANK PAGE

Small Vessel Prostheses

BEST COPY AVAILABLE

BLANK PAGE

TUFTS NEW ENGLAND MEDICAL CENTER
Endothelial Cell Seeding of Small Vessel Prostheses
GRANT NUMBER: 5 R01 HL 28855-03

The overall objective of this project is to determine the effect of endothelial cell seeding on the thrombogenicity and healing of small caliber grafts in primates. Endothelial cells were enzymatically harvested from baboon cephalic veins and cultured in medium supplemented with fetal calf serum, bovine endothelial cell growth factor, and porcine heparin. Endothelial cells were characterized by morphology, immunochemistry, and prostacyclin production. Eight baboons received 17 knitted Dacron carotid interposition grafts in a paired graft experiment. In addition, seven PTFE grafts were implanted when the Dacron grafts were harvested. One graft of each pair was preclotted with blood containing media, the other with blood containing media with $3\text{-}7\text{x}10^6$ autogenous endothelial cells. Platelets were isolated, labeled with Indium-111, and their accumulation on grafts monitored 24 hours after injection with static gamma camera scans at 24 hours, 2, 3, and 4 weeks postimplantation. Grafts were harvested at approximately 5 weeks postimplantation and examined using light and electron microscopy. Endothelial cell seeding significantly ($p < .05$) reduces the platelet reactivity of Dacron grafts 2-4 weeks after implantation, but the effect was small. When compared to paired control grafts, seeded grafts had (a) a more cellular lining, (b) less fibrin coagulum, and (c) more endothelial cells lining the lumen. The thickness of the lining of control grafts was generally greater than that of seeded grafts due to the greater accumulation of fibrin coagulum and adherent blood cells. The lining of seeded PTFE grafts was significantly thinner than that of seeded Dacron grafts.

Allan D. Callow, M.D., Ph.D., Principal Investigator

BEST COPY AVAILABLE

INDIANA UNIVERSITY
Endothelial Seeding of Vascular Grafts
GRANT NUMBER: 2 R01 HL 24247 - 01A1

Small artery prostheses with an extensive endothelial surface demonstrate better patency than unlined prostheses. Our efforts to line e-PTFE and Dacron grafts with endothelium in tissue culture have met with only sporadic success. Polyester elastomer (PE) was tested for its capacity to serve as a tissue culture substrate and as a culture lined graft. PE patches were coated with thin layers of gel, thrombin coagulated plasma, and plasma fibronectin. The coated and uncoated patches were inoculated with 43 - 51 cells/mm^2 of human umbilical vein endothelial cells and maintained in tissue culture for 7 - 11 days, while cell growth was analysed by planimetry. Polystyrene tissue culture plates served as the control surface. There was no significant difference in the rate of cell multiplication nor the maximum surface coverage (89 $\pm$ 9 percent) achieved on polystyrene tissue culture plates, bare or coated PE.

Tubes of PE were extruded, cut into segments measuring 4 mm ID and 60 mm in length, and inoculated with 10^6 endothelial cells labeled with ^{111}In 18 hours before testing. The tubes were subjected to gamma camera analysis just before and 60 minutes after implantation in dog carotid arteries. Four dogs (Group I) received allogeneic, canine cells. Group II (N = 4) received human umbical cells and Group III (I.C. = 7) received autogenous cells. Initial cell attachment was 55 percent in Group I, 52 percent in Group II, and 78 percent in Group III. Cell retention after perfusion was 15 percent in Group I, 27 percent in Group II, and 22 percent in Group III. None of these differences was significant.

We conclude that PE is a polymer that supports tissue cultured endothelium, that large percentages of the PE cultured surface can be covered with various types of endothelium within 18 hours of inoculation, and that early losses of cultured cells from PE during in vivo arterial perfusion are caused by other than immune reactions. Future efforts will include an analysis of the causes of early cell loss from the PE surface during in vivo perfusion and attempts to improve the endothelial - PE bond.

John Glover, M.D., Principal Investigator
Malcolm Herring, M.D., Collaborating Investigator

BEST COPY AVAILABLE

MASSACHUSETTS GENERAL HOSPITAL AND HARVARD MEDICAL SCHOOL
Effects of Compliance Mismatch in Arterial Grafts
Grant Number: HL29429-02

The objective of this project is to conclusively demonstrate or rule out compliance as a signficant influence on graft patency. This is to be accomplished by comparing grafts with different mechanical properties but identical flow surfaces.

Using a technique of differential fixation with gluteraldehyde we produced two conduits of equivalent surfaces, as determined by scanning electron microscopy and measurements of critical surface tension and infrared spectroscopy. Their mechanical properties were significantly different, with circumferential compliance being equivalent to either the native artery or synthetic grafts (e.g. PTFE). These conduits were inserted bilaterally in the femoral artery of dogs, resulting in 100% patency for the compliant graft only. Histologically, some stiff grafts were found to contain longitudinal cracks within their walls - whether these cracks protrude to the lumenal surface and are thus responsible for thrombosis in these grafts must be determined before these data are accepted as proof of the compliance hypothesis. Further histological evaluation of the gluteraldehyde fixation model is underway.

Following up on our demonstration of perianastomotic hyperplasia (PHZ), wherein the compliance of artery first increases before dropping to a minimum as one approaches an anastomotic suture line, we have explored the incidence and possible causes of PHZ. We found PHZ in 18 of 21 continuous anastomoses (CON) and 8 of 16 interrupted anastomoses (INT). Despite its greater incidence in CON, the magnitude of the peak compliance, relative to control artery, was equivalent with both suture techniques. Changes in vessel diameter, longitudinal tension and anastomotic compliance have been examined as possible contributors to PHZ; the direct cause of PHZ is still unclear, however. PHZ produces a local mismatch in compliance at the suture line. It has been observed with equal frequency in the presence of compliant and stiff grafts, suggesting that even with a graft of optimal compliance, there may be an influence of compliance mismatch. The possible relationship between PHZ and subintimal hyperplasia at the anastomoses, a cause of frequent graft failure, is being explored.

Principal Investigator: William A. Abbott, M.D.
Co-Investigators: Joseph Megerman, Ph.D., John T. Fallon, M.D., Ph.D.
Research Associate: Jonathan Hasson, M.D,
Consultant: Robert E. Baier, M.D.

BEST COPY AVAILABLE

LOYOLA UNIVERSITY MEDICAL CENTER AND HINES VETERANS ADMINISTRATION HOSPITAL
Application of Arterial Regeneration
GRANT NUMBER: 1-RO1 HL 29268-02 and
7-RO1 HL 32340-01

The clinical efficacy of small vessel prostheses is largely determined by the morphologic and functional characteristics of its elicited cellular reactions.

Interposition of woven absorbable polyglycolic acid (PGA) prostheses, 3.5mm I.D. x 24mm length, into the adult rabbit aortas was followed after seven days by its phagocytosis by macrophages. At two weeks, ultrastructurally primitive mesenchymal cells transgressed the interstices, proliferated for two weeks, and differentiated for three months into myofibroblasts. Those nearer the lumen showed greater smooth muscle characteristics while those more peripherally located were progressively more fibroblast-like. A confluent endothelial-like flow surface was present after two weeks. Sonomicrometric diameter VS pressure relationships of explanted PGA induced regenerated vessels showed elastic characteristics resembling normal arteries. These specimens withstood pulsatile saline infusion to 4000mm Hg systotic and 1200mm Hg mean pressures. Similarly woven dacron prostheses elicited a significantly thinner less cellular reaction with a fibrinous flow surface.

Several compound prostheses of absorbable PGA or polyglactin 910 (PG910) interwoven with or surrounded by dacron demonstrated both a stimulation of transinterstitial cellular migration by the absorbable polymer and an inhibition of migration by even small dacron concentrations. Inner capsular myofibroblast deposition within 100% PGA or PG910 was more extensive than within dacron containing compound prostheses which in time exceeded that within 100% dacron prostheses.

Polydioxanone (PDS) prostheses stimulated a transinterstitial cellular regeneration identical to PGA but developing more slowly. Myofibroblast migration and proliferation again coincided with macrophage phagocytosis of the prosthetic material.

Results suggest a multifactorial interaction between prosthesis and its elicited transinterstitial cellular regeneration which may include a differential induction of macrophage derived growth factor activity.

Howard P. Greisler, M.D., Principal Investigator
Dae Un Kim, M.D., Collaborating Investigator
John B. Price, M.D., Collaborating Investigator
Arthur B. Voorhees, M.D., Collaborating Investigator
Richard Raymond, Ph.D., Collaborating Investigator
Philip B. Dobrin, Ph.D., Collaborating Investigator

BEST COPY AVAILABLE

UNIVERSITY OF ARIZONA
Small Diameter Vascular Prostheses
GRANT NUMBER: 5 RO1 HL29164-03

Vascular grafts composed of acellular vascular matrix (AVM) are prepared by sequential extraction of native vessels (e.g., carotid arteries) with nonionic and ionic detergents. The resulting material (AVM) is free of cells, nuclei and phospholipids. AVM grafts of 3-4 mm ID and 10-15 cm length implanted for 18 months in the carotid position of dogs remain fully patent and thrombus-free. In this report we present our observations on the process of neointima formation in AVM grafts implanted in the carotid position in dogs.

The rate of recellularization of the luminal surface of implanted AVM was measured by infusion of a solution of Evans Blue 2 hours prior to sacrifice. Non-recellularized AVM surface areas stain intensely blue while the recellularized areas exclude the dye and remain unstained. The validity of dye exclusion as an indicator of recellularization was confirmed by light and scanning electron microscopy. Recellularization appears to procede only from the anastomoses, with no evidence of insular recellularization at sites distant from the anastomoses. The degree of recellularization was measured at 1, 3 and 18 months. The rate of recellularization was approximately twice as fast from the proximal anastomosis than from the distal. Based on the 1 and 3 month observations, the proximal rates of recellularization were in the order of 0.9 cm per month, indicating that 15 cm grafts should be fully recellularized in approximately 10 months, and, indeed, 18 month explants were completely recellularized.

The recellularized surface consists of a thin, but multilayered pannus at each of the anastomoses, which rapidly thins to a single cell layer within approximately 1 cm . The cells of the monolayer and the luminal layer of cells over the pannus were positive for factor VIII antigen as indicated by immunohistology, demonstrating that full endothelial coverage was achieved. The neointimal cells appear to be strictly of luminal origin as there was no evidence of cells migrating to the luminal surface from the adventitia. Host cells do invade both the adventitia and the layers of the media directly adjoining the adventitia; but the compact elastin layers of the sub-luminal medial region remain free of host cells. The results described above were obtained with non-crosslinked AVM. Preliminary evidence indicates that glutaraldehyde fixation severely inhibits formation of the neointima.

Klaus Brendel, Ph.D., Principal Investigator
James M. Malone, M.D., Co-Investigator
Raymond C. Duhamel, Ph.D., Co-Investigator

BEST COPY AVAILABLE

SCRIPPS CLINIC AND RESEARCH FOUNDATION
Graft Thrombus Formation in Baboons
Grant Number: 1-RO1-HL-31469

We have examined the effects of changes in platelet age, count, and prior exposure to thrombogenic surfaces with respect to arterial thrombus formation in baboons. In this model, thrombus formation was initiated by Dacron vascular grafts (4 mm x 10 cm) inserted as extension segments into chronic arteriovenous Silastic shunts. Following platelet labeling with ^{111}In-oxine, platelet deposition was measured for 1 hour following blood contact under arterial flow conditions using a scintillation camera. In six animals platelet deposition was assessed serially using fresh grafts inserted for 1 hour daily on 4 sequential days. Platelet deposition was equivalent on all grafts, rapidly increasing 30-50 fold and plateauing by 1 hour. All grafts produced equivalent reductions in circulating platelet count and blood ^{111}In-platelet radioactivity demonstrating that the labeled cells were functionally equivalent to the total platelet population. Between periods of graft placement the remaining platelets survived normally. Platelet destruction by the graft produced a ten-fold increase in plasma levels of platelet factor 4 (PF4) and β-thromboglobulin (βTG) but did not modify either the α-granule (PF4, βTG) or dense granule (ADP, ATP) contents of circulating platelets. Total platelet deposition exhibited a second order dependence upon the circulating platelet concentration, such that a doubling in platelet count between animals produced nearly a four-fold increase in platelet deposition. Heparin anticoagulation (100 U/kg and 1,000/kg) did not affect the extent of initial platelet deposition, although the higher dose reduced maximum platelet deposition by approximately 50%. We conclude that whereas the capacity of platelets to participate in arterial thrombus formation may be altered by antithrombotic therapy, it is not modified by either aging in the circulation or repeated acute exposure to thrombogenic surfaces.

We have also compared the relative capacities and mechanisms of aspirin, dipyridamole, sulfinpyrazone and dazoxiben to prevent arterial thromboembolism in a baboon model. In 136 studies the agents were given twice daily by oral administration both singly and in combination. The antithrombotic efficacy of a given therapy was determined by its capacity to interrupt steady-state platelet utilization induced by thrombogenic arteriovenous cannulae (Biomer polyurethane, 4 mm x 50 cm). When given alone, dipyridamole and sulfinpyrazone reduced the rate at which platelets were utilized by thrombus formation in a dose-dependent manner with essentially complete interruption by dipyridamole at 10 mg/kg/d. In contrast, neither aspirin (2-100 mg/kg/d) nor dazoxiben (20-100 mg/kg/d) decreased cannula platelet consumption detectably despite the striking reduction in the capacity of platelets to produce thromboxane B_2. However, aspirin, but not dazoxiben, potentiated the antithrombotic effects of dipyridamole and sulfinpyrazone in a dose-dependent fashion without changing the pharmacokinetics for any of the agents. Complete potentiation required aspirin at 20 mg/kg/d to be given with each dose of dipyridamole. Since dazoxiben's blockade of platelet thromboxane A_2 production was not associated with antithrombotic potentiation, and since complete potentiation by aspirin required a dose that fully inhibited vascular production of PGI_2, we conclude that aspirin's potentiating effect on dipyridamole is independent of PGI_2 production or inhibition of thromboxane A_2 formation. In addition, since frequent repeated and synchronous dosing of aspirin was necessary, aspirin's potentiating effects appear to be produced by mechanism(s) unrelated to its potent, irreversible inhibition of platelet cyclooxygenase.

Stephen R. Hanson, Ph.D., Principal Investigator
Laurence A. Harker, M.D., Co-Investigator

BEST COPY AVAILABLE

BROWN UNIVERSITY
Bioresorbable Vascular Grafts
GRANT NUMBER: 5 RO1 HL28975-02

Our research hypothesis is that the biological elements of an arterial wall can be reorganized through the natural repair processes which occur in the slowly disappearing scaffold of a bioresorbable vascular graft, and that these repair processes may provide a newly formed vessel of appropriate structural strength, elasticity, and hemocompatibility. The goal of this project is to fabricate and evaluate vascular prostheses made of bioresorbable polymers.

The specific aims for the coming year are four:

a) to continue experiments with subcutaneous and vascular implants made of "triple ply" Vicryl® (a 9:1 polyglycolic acid - poly (D,L-lactic acid) random copolymer) overcoated with a 1:1 composite of poly (D,L-lactic acid) and poly (2,3-butylene fumarate). This project involves subcutaneous implants in mice for the screening of polymer coatings and infrarenal aortic implants of tubular conduits in dogs for evaluation of durability and repair processes.

b) to continue the evaluation of existing and novel homo- and co-polyesters of Krebs-cycle dicarboxylic acids, as well as composites, capable of delaying the rate of in-vivo disintegration of standard bioresorbable polyesters. This project calls for polymer synthesis, fabrication of subcutaneous implants (mice) and retrieval at given intervals for molecular weight determinations and assessment of tissue reaction.

c) to fabricate vascular grafts woven from a continuous thread of 5-0 Vicryl, and control grafts similarly woven of 220 denier, medical grade Dacron. These prostheses will be coated with resorption-delaying polyesters selected through project b).

d) to evaluate woven, coated bioresorbable vascular grafts implanted in the infrarenal aortic position in the dog and in the carotid position in the sheep (with the controlateral artery serving for implantation of a control Dacron graft.) Polymer decay will be evaluated by gel permeation chromatography; tissue reaction by histology, histochemistry, electron microscopy, and characterization of the mechanical properties of the tissue capsule.

Pierre M. Galletti, M.D., Ph.D., Principal Investigator
Tin-Ho Chiu, Ph.D., Co-Prinipal Investigator
Harvey F. Sasken, M.D., M.P.H., Co-Principal Investigator
Peter D. Richardson, Ph.D., Co-Investigator
Paul McMillan, Ph.D., Co-Investigator
Leonard A. Trudell, D.Sc., Co-Investigator

BEST COPY AVAILABLE

BLANK PAGE

Biomaterials

BEST COPY AVAILABLE

BLANK PAGE

UNIVERSITY OF AKRON
Physical Testing of Polymers for
Use in Circulatory Assist Devices
CONTRACT NUMBER: N01 HV 02909

Short-term fatigue tests were developed to evaluate alternate elastomers for use in the rubber diaphragms of blood pumps. This research was conducted primarily at Monsanto Research Corporation (now the Dayton Laboratory of Monsanto Company) and is continuing at the University of Akron. An experimental protocol has been developed to enable the comparison of the fatigue life of newer, developmental elastomers to other research elastomers and to the presently used cardiovascular elastomers. The test procedures can be conducted using relatively inexpensive, commercially available fatigue testers for most of the tests. The results of these tests should be predictive for constant displacement fatigue applications, such as pusher plate blood pumps.

The following test was found to have the highest correlation with both longer-term *in vitro* fatigue tests and also give results consistant with the limited long-term *in vivo* end-use device test results that are available. The test uses five-inch ASTM dog-bone specimens with a one millimeter razor blade cut in the side. The specimens are fatigued at 2 Hz in 37 degree C air. (Many different environments were tested in this program, but air was found to correlate reasonably well with the whole human blood test results.) The test starts with a one percent strain on the samples. After each 24 hours, the strain is increased by one percent. The average strain at failure for each material is used to compare the fatigue life of the elastomers.

I feel that the reasons this test gives predictive results include the following: 1) A low strain, comparable to end-use applications, is used. Thus, the fatigue failure mechanism in this test is more likely the same mechanism occurring in the final product. 2) Starting with a low strain, and increasing the strain allows any "coaxing effect" to occur. [The coaxing effect is primarily seen in metals, where preliminary fatigue at a lower stress increases the ultimate fatigue life at the higher stress.] 3) The average strain at failure is a measure of fatigue life that approximates the critical tearing energy to propagate a crack in fatigue. [Not to be confused with dynamic tear tests.]

A second measure of fatigue life can be obtained using the same test without the starting cut. [Start at 50 percent strain and increase the strain by 5 percent each day.] Although not as predictive as the above test, this test can provide additional information that may be useful for homogeneous elastomers in applications in the absence of stress concentrators .

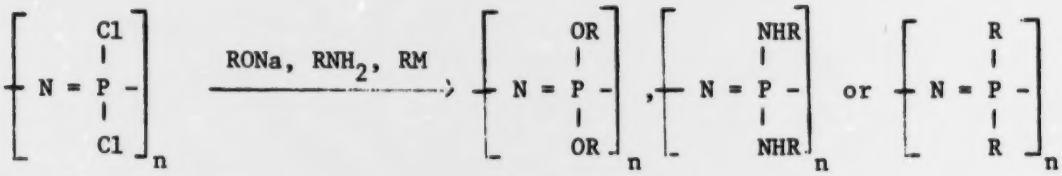
Carl R. McMillin, Ph.D., Principal Investigator

BEST COPY AVAILABLE

THE PENNSYLVANIA STATE UNIVERSITY
Poly(organophosphazenes) for Biomedical Uses
5 R01 HL11418-15

The use of synthetic polymers to solve biomedical problems is an important and growing part of biotechnology. Our objective is to pioneer new synthesis methods that will lead to entirely new polymers of special interest in biomedicine. These fall into two groups, (a) biostable polymers that will be inert in a living system, and (b) bioactive polymers that can be used to mediate biochemical reactions or facilitate the delivery of chemotherapeutic agents.

Our synthetic approach is unusual. It makes use of a reactive inorganic high polymer (I) as a substrate for reactions with a wide range of organic reagents to generate high polymers with diverse properties that depend on the organic side group introduced.



I

(R = alkyl or aryl)

Subsequent chemistry carried out on the organic side groups allows further modification of the properties. Specific side groups (amino acid esters or imidazolyl) stimulate hydrolytic breakdown of the polymer and yield candidate materials for bioerodable, slow release systems. Other side groups (CF_3CH_2O or C_6H_5O) confer biostability and bioinertness character.

In recent work, we have extended the boundaries of this field into the immobilization of catecholamines, steroids, antibacterial agents, and enzymes, and have begun to examine the utility of these polymers as membranes for use in biomedical devices.

Harry R. Allcock, Ph.D.
Principal Investigator

BEST COPY AVAILABLE

WASHINGTON UNIVERSITY
Erythrocyte Deformability and
Vascular Pathophysiology
GRANT NUMBER: 5 RO1 HL 12839

Erythrocyte deformability is believed to be an important factor in microvascular function and is being widely investigated under both static and dynamic conditions. The overall objective of this project is to extend current knowledge of the deformability of normal and diseased erythrocytes with emphasis on those properties which govern the individual cell's capacity to change shape in response to rapidly varying flow patterns. Of particular interest are the physical/chemical changes in erythrocytes which may result in their sequestration in the spleen and other organs *in vivo*.

The experimental approach is to subject age-fractionated populations of normal and diseased cells to well defined shear flows in the rheoscope, a viscometric device consisting of counter-rotating cone and plate. By means of still photography and videotaping, the steady state motion and deformation of the cells are recorded and also their shape recovery following abrupt flow cessation. These observations are being coupled with appropriate mathematical models in an effort to compute elastic and viscous moduli of the erythrocyte membrane. Simultaneous physical and chemical assays (mean cell volume and hemoglobin concentration, membrane phospholipid and protein, glycosylation, etc.) are carried out in a search for correlates of impaired deformability.

Current investigations are focussed on (1) erythrocytes from diabetics in poor metabolic control and with proliferative retinopathy, (2) erythrocytes parasitized by different strains of malaria (*plasmodium berghei* and *cynomolgi*) and by babesia, (3) erythrocytes from hypercholesteremic rabbits, (4) erythrocytes from humans with G6PD deficiency. In parallel with the rheoscope studies, determinations of *in vivo* sequestration in the spleen and other organs of the rat are being examined as a means of verifying physiologic significance of *in vitro* indications of impaired deformability.

S. P. Sutera, Ph.D., Principal Investigator
R. A. Gardner, Ph.D., Project Leader
J. R. Williamson, M.D., Project Leader

BEST COPY AVAILABLE

RICE UNIVERSITY
Flow Effects on Leukocyte Function and Surface Adhesion
GRANT NUMBER: 5 R01 HL 17437-08

The objectives of this research project remain to quantify the effects of mechanical forces on each of the various populations of leukocytes and to examine biochemical modification of these functional alterations. In addition, using a direct video microscopy visualization technique, we plan to examine flow effects on leukocyte adhesion to surfaces coated with purified proteins and endothelial or smooth muscle cells. The biochemical control mechanism of this process is also being investigated.

The development of delayed coagualtion abnormalities after surgery is a significant clinical problem. One possible cause is expression of monocyte tissue factor activity (TFA), stimulated by mechanical trauma or artificial surface interaction. In this study leukocytes and seperated leukocyte fractions were exposed to controlled mechanical trauma in vitro, which in turn caused TFA generation in certain of the sheared samples. The presence of lymphocytes appeared to be necessary for the direct shear stress induced expression of TFA. However, all sheared cells retained their viability and ability to produce TFA, because if stimulated with endotoxin, significant TFA was assayed. Furthermore, at shear stresses comparable to those found in extra-corporeal circulation and in artificial heart valves, significant leukocyte TFA could be induced 24 hours after the mechanical trauma exposure. In addition, this study supports the conclusions of other investigators of a lymphocyte dependent pathway and a lymphocyte independent pathway for TFA production by monocytes.

A modified Couette Viscometer was used to study the effect of shear stresses on human lymphocyte function including proliferative responses to phytohemagglutinin-P (PHA-P), interleukin-2 (IL-2) synthesis, cell viability, cellular enlargement and cell density. Shear stress levels investigated were similar in magnitude to those found in blood pumps and dialysis units. At shear stress levels of 100 and 200 dynes/cm^2 for 10 minutes, a portion of the mononuclear cell suspension was lethally damaged. Shear stressed cells when cultured at 1 x 10^6 cells/ml did not incorporate significant amounts of thymidine into their DNA nor synthesize detectable levels of IL-2. They also did not exhibit the characteristic cellular enlargement induced by PHA. In contrast however when the shear stressed cells were cultured at decreased cell densities of 0.5 x 10^6 and 0.25 x 10^6 cells/ml they incorporated significantly greater amounts of thymidine along with a concomitant increase in synthesis of IL-2. The data suggest that a fraction of cells were shear stress damaged and that such damage inhibited the proliferation of the other cells in a density dependent manner.

BEST COPY AVAILABLE

The flow chamber for surface/leukocyte interaction visualization, with surfaces coated with either specific proteins or endothelial cells, is placed on a temperature-controlled epifluorescent microscope stage. It is then connected to a constant head flow loop. This system is a constant pressure drop loop, with a variable resistance to introduce pulsatility, if desired. The volumetric flow rate is determined by the height of the upper reservoir above the stage, and is directly measured with an electromagnetic flowmeter. The upper reservoir has two outlets - one to the flow chamber and an overflow bypass directly to the lower reservoir. The flow from the return line (through the roller pump) is maintained slightly greater than the flow through the chamber, always assuring some overflow in the upper reservoir, and thus a constant pressure drop across the flow chamber. The volume of the loop has been made as small as 8 ml. Experiments can be run on time scales of minutes or hours. Events are recorded on videotape using a video camera with image intensifier, either in real time or using a time-lapse video recorder.

In order to visualize leukocyte-vessel wall interactions in whole blood, the PMNL were labeled and epifluorescent video microscopy employed. The antimalarial drug quinacrine dihydrochloride (Quin) was used as the fluorescent lable. It is actively taken up into PMNL granules and does not label the nuclear material. Labeling concentrations are 1 - 10 μM. At these concentrations, Quin does not affect PMNL chemiluminescence, chemotaxis, adherence to nylon fibers, or granule release. The excitation wave length is 440 nm with an emission maximum of 505 nm, allowing the use of standard fluorescein isothiocyanate (FITC) filters if necessary. Labeling of erythrocytes is negligible at these concentrations, or at least any fluorescence from red cells is quenched by intracellular hemoglobin. Interestingly, Quin does label the nucleus of lymphocytes, allowing their visualization if desired. If excess Quin is used, endothelial cells will also become fluorescent.

Larry V. McIntire, Ph. D., Principal Investigator
Suzanne G. Eskin, Ph. D., Collaborating Investigator
Bill Brinkley, Ph. D., Collaborating Investigator

BEST COPY AVAILABLE

UNIVERSITY OF UTAH
Initial Events in Thrombus Formation on Surfaces
Grant Number: 5R01-HL-17623-11

It was shown that albumin-heparin conjugate has heparin like activity as determined by APTT, Factor Xa and thrombin time assays. After precoating polymers with albumin-heparin conjugates a strong prolongation of both the plasma recalcification time and whole blood clotting time was observed, indicating that surface induced coagulation is inhibited. Although some release of the conjugate occurs, it was found that the adsorbed albumin heparin conjugate caused prolonged clotting times and that its activity, like heparin in solution, is dependent on complex formation with antithrombin III.

Besides surfaces induced coagulation, platelet adhesion is being evaluated using ex vivo cells. The results indicated that albumin-heparin conjugate preadsorbed surfaces reduced initial blood platelet adhesion. This suggests that an albumin-heparin conjugate can be used for the improvement of the intrinsic blood compatibility of all kind of materials which are used in contact with blood. Less platelet adhesion was observed when the surface was coated with the conjugate of albumin-LMW, high ATIII affinity heparin.

In additon, basic studies on heparin binding to fibrinogen and fibronectin are being carried out using various fractions of heparin separated in this laboratory. Heparin-albumin conjugates and heparin bound fibronectin are utilized for their adsorption onto polymer surfaces.

The ex vivo shunt experiments are underway to evaluate the adsorbed albumin-heparin conjugate contacting with whole rabbit blood.

Sung Wan Kim, Ph.D. Principal Investigator
Jan Feijen, Ph.D. Co-Investigator
Teruo Okano, Ph.D. Co-Investigator

BEST COPY AVAILABLE

UNIVERSITY OF WASHINGTON
Cell and Protein Reaction With Foreign Materials
GRANT NUMBER: HL 19419-08

The work performed on this project since the original proposal was submitted has largely focused on the behavior of fibroblasts, macrophages, and platelets on solid surfaces in relation to the adsorption (from complex, relevant media) of certain proteins thought to influence this behavior (fibronectin, immunoglobulin G, fibrinogen, and von Willebrands factor (VWF). We have been able to show a linear correlation between the amount of fibronectin adsorbed from serum to surfaces and the spreading of 3T3 cells, even though the amount of adsorption and spreading vary greatly and in non-linear, peculiar ways among the various surfaces and serum concentrations used. A new way to perturb the adsorbed layer, variation in the serum or plasma concentration, has been demonstrated. This "mass action" effect is particularly useful for our cell studies because the resultant adsorption of the proteins is not linearly dependent on the concentration but instead passes through a maximum whose position depends on the type of protein; the type of surface; and the overall concentration of the complex mixture (serum or plasma) in characteristic and reproducible ways. Since the cellular response to surfaces treated with varying serum or plasma concentration may also pass through a maximum or assume some particular shape at the same conditions seen for a particular protein, we can probably conclude that the cell is in fact being controlled by the adsorbed amounts of that particular protein. This has in fact been observed for 3T3 cells and fibronectin and we are now working on the macrophage - Ig G/complement C3 and platelet-fibrinogen/VWF systems to ascertain the generality of this phenomena. If it is seen in all these diverse systems, the major hypothesis of this work, that the organization of the adsorbed layer dictated by the surface properties of a material dictates cellular response, will have been established. The significance of this demonstration would be to provide strong evidence for a central mechanism in the response of tissue to foreign surfaces. Since the rational design of improved biomaterials awaits any insight into mechanisms involved in cell-surface interactions, the work here may prove highly significant. Complement activation studies begun before the current period have also been completed and show a correlation between complement activation and HEMA content in the HEMA-EMA copolymer series. We have incidentally discovered a way to greatly enhance fibronectin adsorption with a rather simple and generally applicable technique, namely plasma discharge treatment in the presence of ethylene oxide. This may prove useful in modifying the surface regions of implants to enhance growth and "healing in" of the surrounding tissue (e.g., vascular grafts).

Thomas A. Horbett, Ph.D., Principal Investigator
Buddy D. Ratner, Ph.D., Investigator
Allan S. Hoffman, Sc.D., Investigator

BEST COPY AVAILABLE

UNIVERSITY OF UTAH
Novel Approach to Nonthrombogenic Polymer Surfaces
5 RO1-HL-20251-08

The immobilization of heparin using alkyl spacer arms was carried out to optimize yield on polyurethane surfaces. Heparin releasing polyurethane was also studied to compare its biological activity with the immobilized system.

Immobilized heparin retained its ability to bind and inactivate thrombin and Factor Xa. It was verified that such activity cannot be attributed to the leakage of bound heparin.

Heparin-immobilized polyurethane catheters implanted in canine femoral and jugular veins for one hour periods exhibited significant reduction in thrombus formation compared with untreated polyurethane contralateral controls. The catheters coated with a 9% heparin dispersion in polyurethane were capable of releasing active heparin for several hours, providing even greater improvement in antithrombogenicity. Both types of heparinized surface displayed reduced platelet aggregation and fibrin formation, although platelet adhesion was somewhat higher on the heparin immobilized material than on the heparin-releasing surface.

A dual pharmacological approach to prevent thrombus formation and prevent platelet aggregation was achieved by directly coupling PGE_1 to heparin. The mixed anhydride method was performed using C^{14}-$PGF_{2\alpha}$ as a model. Elution profiles on gel permeation chromatography columns showed coupling of $PGF_{2\alpha}$ onto heparin to the extent of 4×10^{-8} moles $PGF_{2\alpha}$ per milligram Heparin (14.2 μgm $PGF_{2\alpha}$/mg Heparin). Studies were performed to assure that $PGF_{2\alpha}$ was covalently bound to heparin, rather than physical adsorption (leakage studies).

PGE_1 was attached to heparin, based on the results of the pilot C^{14}-$PGF_{2\alpha}$ studies. Preliminary studies (in vitro) indicate the complex will be able to prevent thrombus formation, based on APTT studies and prevent ADP induced platelet aggregation (rabbit model).

Sung Wan Kim Ph.D. Principal Investigator
Teruo Okano, Ph.D. Co-Investigator

BEST COPY AVAILABLE

BOSTON UNIVERSITY MEDICAL CENTER
Hemodynamics in Vascular Surgery
GRANT NUMBER: 3-RO1-HL21796-07

Failure of prosthetic arterial grafts usually occurs between 1 and 18 months following implantation. Early studies demonstrated hyperplasia to occur at the anastomosis between prosthetic graft and host artery. However, the precise role of anastomotic hyperplasia in graft failure has not been delineated.

We have studied the fate of prosthetic arterial grafts in the dog model. Quantitative analysis showed that anastomotic hyperplasia occurred at both the proximal (upstream) and distal (downstream) anastomoses. In our model there was significantly greater hyperplasia at the downstream anastomosis where it was the cause of all delayed Dacron graft failures. The primary localizing factor appears to be the downstream location. We constructed in vitro plastic models to study the flow disturbances at proximal and distal anastomoses. A comparison of those studies with our in vivo results indicates that flow disturbances, especially boundary layer separation, appear to play only a minor role in the development of anastomotic hyperplasia.

We hypothesize that downstream anastomotic hyperplasia is a result of contact activation of blood by the artificial surface, perhaps involving the release of platelet derived growth factor. We have investigated this by placing long Dacron arterial grafts in dogs. Blood samples drawn across the length of the graft demonstrate a measurable increase in Thromboxane B2 and Fibrinopeptide A. Release of these substances is most marked immediately after placement of the Dacron graft. By 7 days it has decreased markedly and remains stable thereafter. Flow reduction caused a marked increase in the release of TXB2 and FPA and there appears to be a critical flow rate, which triggers this release.

Further studies will be directed at comparing different prosthetic graft materials in terms of their propensity to develop downstream anastomotic hyperplasia and to cause release of TXB2 and FPA. The influence of antiplatelet agents on these endpoints will be determined.

Frank W. LoGerfo, M.D., Principal Investigator
Christian Haudenschild, M.D., Collaborating Investigator
C. Robert Valeri, M.D., Collaborating Investigator
Ralph C. Ito, Ph.D., Collaborating Investigator

BEST COPY AVAILABLE

DEPARTMENT OF MEDICINAL CHEMISTRY
AND DEPARTMENT OF MEDICINE
UNIVERSITY OF TENNESSEE CENTER FOR
THE HEALTH SCIENCES, MEMPHIS,
TENNESSEE
Surface-Active Antithrombotic Agents
for Prostheses
GRANT NUMBER: 5-R01-HL-22236-06

The work on novel platelet aggregation inhibitors continues to be rewarding. U.S. Patent 4,443,450 was issued April 17, 1984. Two other American patents are pending; also pending are eleven foreign patents on five continents. The basic premises of our findings are summarized in Blood Platelet Function and Medicinal Chemistry (Lasslo, ed.), New York, Elsevier, 1984, pp. 252-263 and 270-273; cf. Lasslo, Federation Proc., 43:1382-1389,1984; Lasslo and Dugdale, Proc. Cardiovasc. System Dynam. Soc., in press.

More recently, additional observations have been reported on the effect of our compounds on human blood platelet function (Lasslo et al., Biochim. Biophys. Acta, 772:84-92, 1984), and their impact on polymer-induced platelet clustering and retention was examined (Lasslo et al., Med. Prog. Technol., 10:71-88,1984).

The effect of one of our most potent compounds on human blood platelet structural physiology further substantiated our interpretation of the mechanism by means of which our carbamoylpiperidine derivatives exert their action. This congener exerts, indeed, stabilizing action on platelets at the level of the dense tubular system in surface membrane complexes known to sequester platelet calcium. It appears to reinforce, thereby, membrane surfaces interacting with the external environment, rather than by acting on critical sites in the interior of the cell (Lasslo and White, Biochim. Biophys. Acta, in press).

Andrew Lasslo, Ph.D., Principal Investigator
Marion Dugdale, M.D., Co-Principal Investigator

BEST COPY AVAILABLE

BAYLOR COLLEGE OF MEDICINE
Response of Cultured Endothelial Cells to Flow
GRANT NUMBER: 2 R01 HL 23016-06

The qualitative and quantitative nature of the physical forces accompanying blood flow that vascular endothelial cells can withstand is not known. However, it has become increasingly evident that hemodynamic shear stresses have an important role in both the normal physiology and the pathobiology of vascular endothelium.

In order to simulate the hemodynamic environment of the circulation and examine the effect of various fluid shear stresses on the endothelium, we have developed a constant head flow apparatus to subject cultured cells to steady as well as pulsatile shear stress. Human umbilical vein endothelial cells varied their prostacyclin production, microtubule structure, cell shape, and cell orientation with time under shear stress.

Prostacyclin production increased sharply with the onset of steady flow (10 dynes/cm^2), then decreased to an average of 61 $\pm$ 8 pg/10^6 cells/min. Endothelial cells subjected to pulsatile flow (8-12 dynes/cm^2, 1 Hz) showed a similar initial peak in prostacyclin production but leveled off to a steady state production rate (at 6 hours) which averaged 2.2-fold higher (136 $\pm$ 70 pg/10^6 cells/min) than cells subjected to steady flow.

Compared to bovine aortic endothelial cells, human umbilical vein endothelial cells resist alignment under 50 dynes/cm^2.

Cells in only 4 of 15 experiments aligned parallel to the direction of flow within 48 hours, whereas alignment required 24 hours in most experiments on bovine cells.

Labeling of the cells with fluorescently tagged anti-tubulin revealed a full cytoplasmic microtubule complex in the cells subjected to shear stress. The microtubules in the aligned cells were always parallel to the long axis of the cell, whether or not the cell's long axis was parallel to the flow direction.

In order to simulate the influence of pressure on the vascular endothelial and smooth muscle cells, we have designed an apparatus which uniaxially stretches the cells after growing them on a compliant substrate (Mitrathane^R, Mitral Medical International). Both smooth muscle cells and endothelial cells align perpendicular to the axis of stretch (10% strain, 1 Hz, 3 days).

These studies suggest that shear stress and strain play significant roles in endothelial and smooth muscle cell structure and function.

Suzanne G. Eskin, Ph.D., Principal Investigator
Christopher L. Ives, Ph.D., Research Associate
Larry V. McIntire, Ph.D., Collaborating Investigator
Charles L. Seidel, Ph.D., Collaborating Investigator

BEST COPY AVAILABLE

BATTELLE COLUMBUS LABORATORIES
A MOLECULAR LEVEL APPROACH TO BLOOD MATERIALS INTERACTION
Grant NUMBER: 1 RO1 HL 24015-06

Past work has shown that spectra of adsorbing proteins from protein solutions (including blood) can be obtained in virtually real time by the use of attenuated total reflection, Fourier transform infrared spectroscopy. A dual channel cell has been designed that is suitable for flow studies at linear rates approximating those in a medium sized artery. The cell can be used in a chronic shunt with an awake, intact, non-anticoagulated animal. Recent and planned emphasis has been on (a) the more detailed interpretation of the complex spectra, (b) compensation for the spectral contribution of the bulk, non-adsorbed proteins which in the case of blood exceeds that of the adsorbate, and (c) the identification and the effect on the protein adsorption of low molecular weight species in blood which diffuse to the surface before the proteins. This last effort arises from earlier observations that in the first minute of exposure of a surface to blood, IR adsorption bands not corresponding to any major proteins have been seen before albumin of other plasma proteins appear. These bands have been shown to arise from species with molecular weight less than approximately 1000 Daltons, which is in accord with the faster diffusion rate enabling them to be seen before the proteins. There are indications that one or more of these small compounds, through their earlier arrival and adsorption, modify the adsorption of the proteins and thus can be of importance in blood-material interaction. Efforts are underway to identify these compounds and determine their influence on the adsorption of blood proteins on foreign surfaces.

Robert I. Leininger, Ph.D., Principal Investigator
David J. Fink, Ph.D., Co-Investigator
R. Michael Gendreau, M.D., Co-Investigator
Timothy B. Hutson, Co-Investigator
Robert J. Jakobsen, Co-Investigator

BEST COPY AVAILABLE

DIVISION OF LABORATORIES AND RESEARCH, NEW YORK STATE DEPARTMENT OF HEALTH
Blood-Materials Interactions: The Bridge Problems
GRANT NUMBER: 5 R01 HL 24017-06

A wide variety of physical and chemical agents have been screened for effects on platelet retention from native whole blood and on platelet adhesion from citrated whole blood flowing through conventional glass bead columns. Spontaneous and chemically-induced detachment of platelets from these columns into flowing or gently mixed anticoagulated blood, hard-spun plasma, or saline has also been studied. Paradoxically, agents which induce platelet aggregation in platelet-rich plasma (PRP) inhibited retention (platelet/plasma multilayer formation) and also depressed the rate of the primary phase of adhesion (monolayer formation). The phenomenon seemed equivalent to the transient refractory state of stimulated platelets when collisions are minimized as occurs in unstirred or diluted PRP. Glucosamine and colchicine, which are known to inhibit fibrinogen binding by stimulated platelets, completely abolished the primary phase of adhesion. In addition, agents which directly affect (EDTA) or compete (glucosamine) for the fibrinogen receptor or cleave (Ancrod) fibrinogen promoted detachment.

The results further support the concept that fibrinogen "bridges" to the substrate and between platelets are important to both adhesion and retention in glass bead columns.

W. Jean Dodds, D.V.M., Principal Investigator
John A. Bergeron, Ph.D., Co-investigator

BEST COPY AVAILABLE

UNIVERSITY OF TORONTO
Fate of Surface Bound Heparin
GRANT NUMBER: 5 ROI HL 24020-06

This research has been focussed on the interactions of surface bound heparin with blood, with particular emphasis on testing the validity of the concerns of critics regarding the use of heparinized materials in long term applications: (1) a heparin microenvironment is necessary (2) saturation of the heparin occurs (3) enhanced consumption of clotting factors and (4) platelet activation is augmented.

For work heparin is immobilzed onto polyvinyl alcohol via its terminal serine. The heparin is released too slowly ($\sim 10^{-4} \mu g/cm^2 \cdot min$) to create a microenvironment at the blood interface so that the observed in vitro (PTT, thrombin time, chromogenic substrate) and ex vivo (parallel flow AV shunt) thromboresistance must be attributed to the ability of the bound heparin to potentiate the antithrombin III (AT III) inactivation of thrombin. The surface bound heparin on a heparin-PVA coated polyethylene (PE) tube is able to retain its biological activity. The bound heparin appears to act catalytically, and is not consumed by prior exposure to thrombin and antithrombin III. ^{125}I-thrombin-antithrombin III complexes, formed on heparin-PVA beads, were displaced from the beads by defibrinated plasma but not by phosphate bufferred saline (pH 7-4, PBS).

There was little significant difference in the number of platelets adhering to heparin-PVA and PVA gels without heparin in a static test with washed porcine platelets, in the Feuerstein Flow system with washed human platelets in the degree of release by the washed human adherent platelets or in bead column retention with citrated canine whole blood. Therefore we hypothesize that surface bound heparin per se has little impact on platelet activation. Rather it appears that the underlying surface (here PVA) dominates the interaction of the material with platelets and that its platelet reactivity determines the extent of release and aggregation.

To improve the (short term) platelet compatibility of PVA and heparin-PVA, PGI_2 or PGE_1 is to be immobilized, the former using a method similar to Ebert et al (J. Biomed. Mater. Res. 16, 629, 1982).

We continue to focus on the behaviour of platelets in contact with heparinized tubing since this is the critical concern regarding its use in the cardiocirculatory assist devices and blood handling procedures that await the development of blood compatible materials.

Michael V. Sefton, Sc.D. - Principal Investigator
Mark W.C. Hatton, Ph.D. - Coinvestigator
Walter Zingg, M.D. - Coinvestigator

BEST COPY AVAILABLE

CASE WESTERN RESERVE UNIVERSITY
Long Term Biodegradation of Elastomeric Biomaterials
Grant Number: 1-RO1-HL-25239-05

The goal of this project is to determine the effect of the physiological environment on the long-term stability of polymeric biomaterials. This study examines the effect of *in vitro* exposure to enzymes on the performance properties of Biomer, a segmented polyurethane used in blood contacting devices. Ultrathin films were treated for periods from one to six months at 37°C with two proteolytic enzymes. Papain is similar to cathepsin B, a thiol endopeptidase released during the inflammatory response. Urease is released by leukocytes during the inflammatory response.

A 10-20 percent decrease in number average and weight average molecular weights by gel permeation chromatography was measured after exposure to papain for six months. Detection of free amine and hydroxyl groups by ATR-FTIR indicates that chain cleavage occurs by hydrolysis of both urea and urethane linkages. No change in molecular weight was observed after six months' treatment with urease. Nevertheless, the appearance of free amine absorptions by ATR-FTIR is strong evidence that surface degradation has occurred. Since the molecular weight of urease is 473,000 compared to 20,700 for papain, urease action appears to be confined to the surface whereas the bulk of the polymer film is accessible to papain.

The treatment had no significant effect on the modulus, the ultimate tensile strength or the fracture strain. This is not surprising since above 40,000, the critical value, these properties are not sensitive to molecular weight. Nevertheless, exposure for longer periods of time could result in deterioration of the tensile properties. Undesirable consequences were observed in mechanical tests which measured cumulative damage effects. The high strain fatigue lifetime was shortened considerably by treatment with either urease or papain. This effect is attributed to premature initiation of macroscopic cracks at surface defects caused by degradation.

Efforts to examine the cellular biocompatibility of various biomedical polymers continue. The biocompatibility of low density polyethylene and a cytotoxic polyvinylchloride have been investigated using the *in vivo* cage implant system. The cytotoxic polyvinyl chloride stimulated an intense acute phase inflammatory response and at later times, an intense and increasingly chronic inflammatory response. This system is being used to investigate the stability of Biomer and other candidate blood-contacting polymers under accelerated inflammatory conditions. Cellular biocompatibility studies of the NHLBI reference materials are currently under investigation.

P. Anne Hiltner, Ph.D., Principal Investigator
James M. Anderson, M.D., Ph.D., Co-Investigator

BEST COPY AVAILABLE

UNIVERSITY OF WASHINGTON
Surface and Bulk Structure of Polyetherurethanes
GRANT NUMBER: 2 RO1 HL 25951-04

The central hypothesis of this program is that the surface structure of polyetherurethane (PEU) polymers is an important and systematic determinant of the blood compatibility of this class of polymers. Since the surface structure and the bulk structure of PEU's are usually different, if we can understand the factors that influence the surface structure, we can rationally design more blood compatible PEU's. Major projects have been initiated in the areas of synthesis, surface characterization, and biological reaction to PEU's. Synthetic projects involve the synthesis of two classes of PEU materials with alternate soft segment blocks, PEU-poly(dimethyl siloxane) and PEU-poly(alkyl methacrylate), and one PEU with a fluorinated hard segment. These will be studied for molecular weight distribution, and surface segregation. Also, new polyurethane surfaces have been prepared via the addition of low molecular weight materials into polyurethane casting solutions. The surface properties of these blends are investigated by ESCA, and peel strength measurements. Finally, the biological properties of the PEU's synthesized under this program are being studied via protein adsorption measurements, laser light scattering emboli detection and in vitro cell culture experiments. The cell culture measurements suggest that PEU's can be synthesized that induce the lysis of cell membranes. The significance of this observation is under investigation.

Buddy D. Ratner, Ph.D., Principal Investigator
Amarjeev Kaul, Ph.D., Investigator

BEST COPY AVAILABLE

STANFORD UNIVERSITY
PAA Adsorption on Polymers Using TIRF and FTIR/ATR
GRANT NUMBER: 2 RO1 HL 27187-04

The interactions of proteins with solid surfaces are complex and not well characterized. Factors requiring study include adsorption and desorption kinetics, equilibrium between surface and solution proteins, and conformational aspects of the adsorbed protein layer.

Total internal reflection fluorescence (TIRF) is a technique especially well suited to the *in situ* study of protein/surface interactions. In TIRF, an evanescent wave, generated at the point of total internal reflection of a laser beam directed at an interface between two transparent media with differing indices of refraction, is used to excite fluorescent molecules close to or adsorbed to the interface.

Our work began with the development of a TIRF apparatus, which was used in preliminary studies of the adsorption of bovine serum albumin (BSA), fibrinogen, and γ-globulin onto silicone rubber. This work was continued with the construction of a second generation TIRF apparatus. The adsorption of BSA and fibrinogen onto crosslinked polydimethylsiloxane (PDMS) from flowing solutions was examined. These studies established TIRF as a useful tool in the investigation of protein adsorption phenomena. The application of TIRF to the study of competetive adsorption was also demonstrated with studies of adsorption from BSA/fibrinogen mixtures.

The relationship between surface properties and the kinetics of adsorption was then investigated. The adsorption of BSA onto six surfaces exhibiting a wide range of surface functionalities was studied. The results were compared to a mathematical model describing the hydrodynamic environment at the adsorbing surface in order to quantitatively determine the effects of mass trnasport limitations on the adsorption process. It was found that the observation of intrinsic protein adsorption kinetics is often confounded by mass transport limitations.

Our current efforts focus on the study of the conformation of adsorbed proteins and its effect on the adsorption process. Preliminary fluorescence polarization studies on an adsorbed BSA layer suggest that, as the bulk solution pH increases above the isoelectric point of BSA, the adsorbed layer expands due to increasing electrostatic repulsion of the BSA molecules. Further studies concerning the conformational nature of adsorbing proteins include investigations of the interactions of antibodies with adsorbed protein, and the study of the adsorption of small, disulfide rich proteins whose conformations have been altered by disulfidebondreduction.

Channing R. Robertson, Ph.D., Principal Investigator

BEST COPY AVAILABLE

CASE WESTERN RESERVE UNIVERSITY
Human Vascular Grafts: The Blood/Materials Interaction
Grant Number: 1-RO1-HL-27277-03

This project is directed toward obtaining a better understanding of the blood/materials interaction in human synthetic vascular grafts. The studies involve human blood interactions with vascular graft materials and the compositional analysis of the pseudointima that develops on human vascular grafts.

To date, we have completed an extensive biochemical and histological analysis of Dacron vascular prostheses recovered from human recipients. Additional studies on pseudointima/neointima on vascular prostheses from canines are being carried out to provide information on species differences. These studies form the basis for an understanding of those factors which influence pseudointima/neointima development. In recovered human vascular prostheses we have found that in successful Dacron grafts, patent at the time of removal, the collagen content of the pseudointima was low (< 5 percent) but contained an unexpectedly high proportion of type V collagen relative to types I and III. In human grafts stenotic or occluded by fibrous tissue at the time of removal, the fibrous tissue filling the lumen contained primarily type I collagen. In most Dacron grafts, the collagen in the tissue occupying the fabric interstices was rich in type III, relative to the pseudointima or the outer capsule.

A recirculating, in vitro system has been used to study the interaction of human blood with vascular graft materials. Blood samples, taken prior to and during the recirculation were assayed for platelet count, platelet retention ability, platelet factor 3, platelet release (PF4 and βTG levels), platelet aggregation, leukocyte count, complement activation (C5a), prothrombin time, partial thromboplastin time, fibrinogen level and fibrinopeptide A level. Both heparin and citrate have been used as anticoagulants. In a study comparing 8mm ID silicone, ePTFE and crimped, knitted Dacron, Dacron was more platelet and coagulation activating than either ePTFE or silicone, the latter two being similar. This was shown for Dacron relative to silicone by a decrease in platelet count, an increase in plasma PF4 and βTG levels, an increase in platelet factor 3 availability, and an increase in fibrinopeptide A (FpA) levels. With heparin, Dacron showed complement activation concomitant with a decrease in neutrophil count, possibly signalling neutrophil adhesion. The effect of preclotting Dacron on platelet function also has been studied.

This in vitro perfusion system has been adapted to study small diameter (4mm ID) vascular grafts at low flow rates. When ePTFE was compared to silicone, platelet counts for both materials remained near baseline at 100 and 75 ml/min. However, when the flow rate was lowered to 50 ml/min, the platelet count dropped to 70 percent of baseline for the silicone with that for ePTFE remaining stable. Preliminary studies with 4mm ID NHLBI standard reference materials at flow rates of 50, 75, and 100 ml/min show little difference in platelet activation when compared to the silicone rubber used in these experiments.

James M. Anderson, M.D., Ph.D., Principal Investigator

BEST COPY AVAILABLE

UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT DALLAS
Blood Trauma from Microporous Membrane Oxygenators
GRANT NUMBER: 5 R01 HL28690-04

Our research has focused on developing visualization methods to aid in understanding the early events in protein adsorption on blood-contacting materials. We have also devoted considerable effort to developing a novel method for favorably altering the blood compatibility of polymers, treating surfaces to allow preferential binding of endogenous serum albumin.

Visualization of protein adsorption in prior years' work by partial gold decoration- and immunoferritin TEM (for a number of polymers and pyrolytic carbon) has been substantiated this year by conventional radiolabel-based surface concentration measurements. Fibrinogen, and especially albumin films, are more extensive, closely packed, perhaps thicker and bound more tenaciously on pyrolytic carbon surfaces than on typical hydrophobic polymers. The organization of adsorbed protein on hydrophobic polymers is quite different: fibrinogen creates a reticulated network and albumin, sparse microaggregation.

Using commercially feasible surface alkyl- and acylation techniques, Cuprophan and other cellulose derivatives, Dacron polyester, and a number of polyurethane formulations have shown marked increases in albumin affinity compared to underivatized controls. Albumin coats rapidly and densely on the derivatized polymers, compared to slow and sparse microaggregate coatings on controls.

Total internal reflectance fluorescence (TIRF) technique has been perfected, utilizing a pulse nitrogen laser system, allowing us to probe the conformation of bound albumin. Albumin binding experiments (from solution to a quartz substrate) have been completed and produced interesting results. Comparison of fluorescence lifetime in bulk solution and in the surface adsorbed state indicates a statistically significant decrease in quantum yield upon surface adsorption. Quantum yield of albumin in the adsorbed state is similar to that observed in bulk solution at pH 3.8, close to the isoelectric point. Similar quantum yield for bulk albumin solution is observed with heat denaturation of the protein. Similar results were obtained for purified albumin monomer and unpurified Fraction V. Photobleaching and other artifacts which have hampered previous research in this area have been satisfactorily resolved with this instrumentation system. Results suggest that significant alteration of structure (unfolding) accompanies adsorption of albumin on quartz and suggests an interesting series of experiments.

We continue to obtain promising results for small vessel vascular prostheses treated to adsorb and retain serum albumin from blood. Our results provide no conflict with the hypothesis that the hydrophobic interaction between albumin and C_{16} and C_{18} alkylated polymers allows maintenance of a thromboresistive coating of serum albumin for an extended period of blood exposure.

Robert C. Eberhart, Ph.D., Principal Investigator
Frederick Grinnell, Ph.D., Co-Investigator
Morton Prager, Ph.D., Co-Investigator
Mark Munro, Research Assistant
Jack Frautschi, Research Assistant

BEST COPY AVAILABLE

BAYLOR COLLEGE OF MEDICINE
Effects of Shear Stress on Red Blood Cells
GRANT NUMBER: 5 R23 HL 30834-02

Red blood cells are subjected to shearing forces as a result of circulation through artificial devices such as cardiopulmonary bypass pumps, renal dialysis units, or circulation through prosthetic heart valves. Red blood cells in the normal circulation probably experience a low level of shear stress that may increase during rigorous exercise. Shear stresses above 1500 dynes/cm^2 have been shown previously to cause fragmentation and hemolysis while subhemolytic shear stresses have been shown to produce a damaged cell marked by decreased deformability and increased calcium content.

We have investigated further the relationship between subhemolytic shear stress, calcium uptake and the observed decreased red blood cell deformability. Red blood cells were sheared in a concentric cylinder viscometer at stresses between 500 and 1500 dynes/cm^2. Deformability was assessed by a Nuclepore filtration technique. It was found that varying the external calcium concentration had no effect on the change in RBC deformability as measured by Nuclepore filtration. RBCs suspended in 2.0 mM calcium were subjected to shear stress in the presence of ^{45}Ca radioactive label. These cells showed a shear stress related uptake of the labeled calcium and also extrusion of the calcium in post shear incubation studies. Furthermore, the presence of equimolar amounts of EGTA, a relatively specific calcium chelator, completely blocked subhemolytic shear induced calcium uptake. RBCs sheared in the presence of calcium and EGTA had the same decrement in deformability that occurred in cells sheared in the presence of calcium without the chelator. This finding suggests calcium uptake resulting from shear stress does not substantially contribute to the decreased deformability of the subhemolytically sheared RBCs.

In addition, we found that the conditions of shear greatly influenced calcium uptake. If cells are sheared in a higher viscosity medium such as dextran, there is a greater degree of calcium uptake by cells, hemolysis and potassium loss than that seen for the same shear stress achieved at higher shear rates when the suspending medium is closer to a physiologic viscosity.

From our studies we conclude that calcium uptake after low levels of shear stress appears to be relatively unimportant as most of this is immediately extruded from the cell. The increased calcium leak is probably secondary to more fundamental alterations in the red cell membrane. The importance of calcium uptake in cells subjected to hemolytic shear stresses or when physiologically impaired red cells of uremic individuals or in sickle cell disease are sheared remains to be seen.

Mark M. Udden, M.D., Principal Investigator

BEST COPY AVAILABLE

UNIVERSITY OF WASHINGTON
Mechanisms of Arterial Graft Failure
Grant Number: 5R01 HL30946-02

Failure of long-term synthetic arterial bypass grafts has been attributed in part to anastomotic stenosis, but the pathological basis for this has not been determined. Which cells participate in the formation of the stenosis and the relationship between normal healing and the pathological development of anastomotic narrowing have not been delineated. In this study we have examined early wound healing in 4 mm polytetrafluorethylene (PTFE) arterial bypass grafts placed in baboons. In this primate model, endothelium and smooth muscle cells (SMC) derived from the cut ends of adjacent artery form the new intima and migrate together along the luminal surface of the graft at approximately 0.2 mm/day. Both cell types proliferate in association with the growing edge. In addition, both endothelium and SMC located discretely over anastomoses continue to proliferate despite complete endothelial coverage. Intimal cross-sectional area in this region is always greater than over adjacent graft. Fibroblasts are invariably found in graft matrix and adventitia and do not contribute to formation of intima. We hypothesize that anastomotic narrowing might be due to chronic endothelial injury and turnover associated with continued SMC proliferation and intimal thickening.

Alexander W. Clowes, M.D., Principal Investigator
Allen M. Gown, M.D., Collaborating Investigator
Stephen R. Hanson, Ph.D., Collaborating Investigator
Michael A. Reidy, Ph.D., Collaborating Investigator

BEST COPY AVAILABLE

BIOMETRIC SYSTEMS,INC.
Anatomical Substitutes with Proclivity for Cell Lining
GRANT NUMBER: 1R43 HL 32382-01

Biomaterials are needed for a wide variety of functions and environments within the body, requiring a wide variety of physical properties for their construction and stable functioning. A major difficulty is found in acquiring a biocompatible surface in combination with the required physical properties (e.g., strength, elasticity, permeability and flexibility) stable over a long period of use in the body. A major advance in biomaterials technology would result from the ability to readily tailor the surface of preformed physically optimized implant devices, to provide the proclivity for rapid overgrowth of a stable natural cell surface lining.

Fibronectin (FN) and laminin (LM) are important polypeptide attachment factors for mammalian cells in culture. These proteins are potent stimulators of cell migration in vitro. FN, LM, and combinations of these proteins are coupled to the surface of prostheses plastics using heterofunctional crosslinking photoreactive reagents. Plastics studied in this project include polyvinyl chloride, polypropiene, polyethylene, polystrene, polyurethane and polytetrafluoroethylene (disks and tubing).

Preliminary studies using Bovine endothelial cells suggest that these factors stimulate cell migration and overgrowth of the surface of artifical vascular plastics. Human endothelial cells will be used in future tests to document regrowth over factor bound matrix on similar plastics. The Canine Model will be used for in vivo bilateral femoral graft studies.

If a non-thrombcgenic human endothelial cell lining were possible, the impact upon modern surgical practice would be signiciant. A non-thrombogenic implantable device would clearly increase the market far beyond the current market.

Peter H. Duquette,Ph.D., Principal Investigator
Ruth B. Johnson, M.S., Collaborating Investigator
Peter Nash, Ph.D., Collaborating Investigator

BEST COPY AVAILABLE

Primary Reference Material

BEST COPY AVAILABLE

BLANK PAGE

MERCOR, Incorporated
A Thoratec Company

PROCUREMENT OF PRIMARY REFERENCE MATERIALS

CONTRACT NO. NO1-HV-92933

The objective of this contract is the fabrication, characterization and distribution of large quantities of silica-free polydimethylsiloxane (PSX) for use as Primary Reference Materials (PRM) by NHLBI designated laboratories to facilitate comparison of test systems and biomaterials data.

In fabricating both the sheet and tubing configurations, silica-free room temperature vulcanizing (RTV) PSX fluid was synthesized and applied to a substrate material under class 100 cleanroom conditions. Sterilized samples from each fabrication lot were subjected to characterization by three bulk and four surface techniques: DSC, TGA, Swelling/Extractables, SEM, ESCA, γc and ATR-IR. A masterfile is kept which documents these results as well as the process conditions and characterization for each step from the synthesis of the RTV through the sterilization of the packaged samples.

Samples from Sheet Lots 03 and 04 and Tubing Lots 01 and 02 have been subjected to quality assurance testing to confirm the stability of the PRM. The testing techniques employed are Equilibrium Swelling/Extractables, γc and ESCA To date all the lots of Sheet and Tubing PRM have remained stable during storage.

ESCA analysis performed on each lot by the University of Utah confirms the chemical purity of the RTV coated surface. Typical ESCA results give the C:O:Si ratio of 2:1:1 as expected for pure polydimethylsiloxane.

Upon notification from NHLBI, samples are distrubuted to the investigators. Included with each shipment is a package insert containing a brief description of the material, handling and storage conditions, characterization report forms, current quality assurance testing results and a brief description of the characterization methods used.

BEST COPY AVAILABLE

To date, polydimethylsiloxane PRM have been distributed to 15 investigators in 5 countries.

At the completion of this contract, September 31, 1984, MERCOR, Incorporated will continue to distribute the remaining 23,000 polydimethylsiloxane Primary Reference Materials.

Robert S. Ward, Prinicpal Investigator
Kathleen A. White, Analytical Chemist

BEST COPY AVAILABLE

Mechanical Circulatory Support: Energy Transmission

BEST COPY AVAILABLE

BLANK PAGE

THERMEDICS INC.
(New England Medical Center)
Research and Development of Systems for
Transmitting Energy Through Intact Skin
CONTRACT NUMBER: N01-HV-02903

A Transcutaneous Energy Transmission (TET) system has been developed to deliver electric power to permanent implanted Ventricular Assist Systems (VAS's) and Total Artificial Hearts (TAH's) without passing conductors through the skin. The TET system inductively couples energy between a superficial coil of wire resting on the skin surface and a coil implanted 1.5 cm deep. Together the coils form a "transcutaneous transformer". The system offers an alternative to percutaneous power leads, effectively buying a solution to the problem of infection at the site of a large diameter percutaneous access device with increased electrical complexity and decreased energy transfer efficiency.

The transcutaneous transformer is a loosely coupled air core transformer. The implanted (secondary) coil contains 16 turns of wire arranged to fit within a desired geometry. The geometry was chosen to produce a shallow mound when the coil is implanted subdermally at a depth of approximately 1.5 cm. The superficial (primary) coil contains 3 turns of wire wound in a flat spiral. The inner diameter of superficial coil was chosen to approximate the perimeter of the mound created by the implanted coil. These mating shapes resist misalignment of the coils which will degrade transformer performance. In humans, an elastic bandage should suffice to hold the lightweight primary coil in place. Proper alignment is readily achieved by non-technical persons.

The implanted coil is a composite structure of carefully chosen materials. The coil is wound from copper Litz wire (3/5/20/38) whose characteristics were selected to minimize coil heating due to I^2R losses. The copper conductors in the wire are protected from degradation by body fluids by a barrier of specially formulated butyl rubber which is highly impermeable to moisture. The butyl-coated coil is encapsulated in a polyether based elastomeric urethane such that surrounding tissues are presented with an abrasion resistnat, non-toxic surface of demonstrated tissue compatibility.

A series of studies were undertaken to: 1) evaluate the biocompatibility of the materials; 2) study the tissue response to the thermal and radiofrequency characteristics of these systems: 3) determine whether the size and shape of these devices were suitable: 4) study the ability of the skin overlying the implanted coil to regenerate if traumatized: and 5) determine the extent to which system migration occurred following implantation. While it was not possible to study each of these considerations in detail, our findings based on tests of 18 systems implanted in 9 Pitmann Moore miniature pigs may be summarized as follows. Essentially no differences were detected

BEST COPY AVAILABLE

in the tissue response between unpowered and actively powered TET systems in experiments ranging up to 22.5 months. The tissue response was typical of a mild, chronic, foreign body reaction to any nonbiologic, implanted object. The implanted secondary coil was "walled off" with a dense collagenous capsule which was generally quite fibrous and only moderately vascularized. The surrounding tissue remained well vascularized and exhibited normal tissue structure, tone, and vitality. The implant site appeared adequately perfused and was observed to regenerate without incidence when injured by animal trauma. The skin surface was characterized by a normal appearing epidermis, unaffected by the presence of the primary coil, and was covered by a normal compliment of hair. No evidence of system sinking or migration was detected up to the 22.5-month period. However, the mound of skin overlying the secondary characteristically lost some of its prominence in cases where the animal's weight increased dramatically.

Based on these experiences, the Series II TET system appears to be well accommodated by the host. The materials, size, shape, thermal, and radiofrequency characteristics of these systems appear satisfactory for long-term transmission of energy.

Craig Sherman, Principal Investigator
Ben Daly, Coprincipal Investigator

BEST COPY AVAILABLE

NOVACOR MEDICAL CORPORATION
(Department of Surgery, School of Medicine,
State University of New York at Stony Brook)
Electrical Energy Transmission Technique Development
CONTRACT NUMBER: NO1-HV-72933

The "belt" skin transformer (BST) consists of a pair of narrow, flexible, concentric coils (located around the waist). It exhibits an inherently high and stable coupling efficiency, and represents an attractive alternative to percutaneous leads for powering permanent implanted cardiac prostheses.

Long-term tissue compatibility, electromagnetic efficacy, mechanical longevity and superior compliance are critical design factors. An integrated secondary and connector development effort led to the final, single-turn, flat, helical configuration. The ten conductors are electrically parallel, nearly eliminating potential gradients between them, or to the surrounding tissue. A small, toroidal step-up transformer matches this low voltage to the VAS load.

Secondary belts of varying geometry, elastomeric materials and connector design have been implanted in a total of 63 dogs. Early experiments were designed primarily to evaluate alternative elastomers. Chemical and mechanical tests of explanted belts, fabricated from several compatible materials, led to selection of Sil-Med SM4050 heat vulcanizing silicone rubber for the secondary encapsulant. Its superiority was borne out by continued excellent secondary performance *in vivo* for periods exceeding the two-year design goal.

Long-term *in vivo* evaluation of complete functional BSTs was conducted in eight animals. An implanted capacitive load permitted chronic secondary excitation at full BST operating power, but without significant intracorporeal heat dissipation. Primary belts having conductors woven into a porous, soft elastic band proved easier to maintain for long periods on dogs and, therefore, supplanted the earlier molded-elastomer primaries. Continuous electrical excitation and BST performance data management were provided by a microprocessor-controlled, central power and data acquisition system.

Only one of the eight long-term secondaries, fabricated from Dow-Corning MDX 4-4210 (the alternative material), failed *in vivo*. In most cases, Sil-Med belts showed little degradation over the test period. In two cases, localized conductor corrosion occurred in the vicinity of small tears or nicks in the elastomer, which may have occurred at implant and did not propagate.

Six of the eight long-term secondaries remained implanted for at least one year. Infection prompted the termination of one experiment, while a second animal was lost to unrelated causes. Excluding these two, the long-term functional BST evaluations averaged more than 20 months, with the longest exceeding 29 months. Explanted belts were typically in excellent condition and enclosed in a thin, compliant, tissue capsule. This experience strongly supports the viability of the belt skin transformer as a suitable power source for long-term circulatory assist devices.

Peer M. Portner, Ph.D., Principal Investigator
Sylvain Pitzele, M.D., Ph.D., Principal Investigator for Subcontractor
David H. LaForge, B.S., Program Manager
George F. Green, Ph.D., Manager, Polymer Chemistry
Frank K. Beering, B.S., Mechanical Engineer

BEST COPY AVAILABLE

SINAI HOSPITAL OF DETROIT
(University of Michigan)
Development of a Percutaneous
Energy Transmission System
CONTRACT NUMBER: NO1-HV-8-2921

To develop a Percutaneous Access Device (PAD) free of infection, through which pneumatic, hydraulic or electrical energy may be transmitted for long periods of time, our group investigated a technique whereby a biological seal between the PAD and the surrounding tissue was established through autologous fibroblasts grown on the transcutaneous portion of the PAD neck. We observed that the fibroblasts form confluent multilayers and extend cell processes into the nanopores in the PAD neck in vitro. Upon implantation of the PAD with such an Autologous Living Coated Nanoporous (ALCON) surface, epithelial migration was usually (in eight out of eleven cases) inhibited for an extended period of time as reported earlier.

At last year's contractors' meeting, we reported a modification in the PAD implantation technique, from a single-stage to a multi-stage procedure, which was designed to improve the consistency of results. Long-term evaluation of PADs using both techniques are proceeding.

Six PADs (including two controls) were implanted using the single-stage procedure and twelve PADs (including two controls) were implanted using the multi-stage technique. One of the control PADs was removed following infection and the remaining three show variable degrees of skin retraction, an early sign of failure, around the implant. In the experimental group, two multi-stage implants had to be removed prematurely, at four and three and a half months respectively, due to trauma of unknown origin in one and erosion of the PAD flange in the other. Histological sections from both clearly demonstrated inhibition of epithelial downgrowth, a result consistent with our previous findings.

The remaining twelve implants appear clinically satisfactory for periods up to 15 months postimplantation to this date. No differences in the results from the two implantation techniques are so far apparent. All implants are scheduled for removal at 24 months postimplantation.

Adrian Kantrowitz, M.D., Principal Investigator
Paul S. Freed, M.S.
Tarik Wasfie, M.D.
Kenichi Hagiwara, M.D.
F.L. Vaughan, Ph.D., Principal Investigator for Subcontract
L.I. Bernstam, M.D.
I.A. Bernstein, M.D.
Robert H. Gray, Ph.D.

BEST COPY AVAILABLE

ST. ELIZABETH'S HOSPITAL - TUFTS UNIVERSITY
(THERMEDICS, INCORPORATED)
Development of Percutaneous Energy
Transmission Systems
CONTRACT NUMBER: NO1-HV-8-2919

Percutaneous energy transmission system development has continued in our laboratories for over six years. Our initial prototype system consisted of five components and four biomaterials (fig. 1.) The carbon coated titanium button was designed to minimize reaction at the epidermis. The porous PTFE was designed to encourage infiltration of connective tissue within its pores and the development of a collagen-biomaterial seal to inhibit epidermal migration and sinus formation. The Dacron velour was designed to promote rapid tenacious bonding in deep tissues. The subcutaneous skirt was to provide strain relief to the system as a whole and to prevent distraction of the epidermis away from the relatively weak tissue - PTFE bond. Our final configuration is seen in fig. 2. With the exception of eliminating the conduit for testing purposes, very few changes in overall design have been made over the years, and our in vivo experience with these systems now consists of 98 implantations in 49 miniature pigs.

Changes in design have included: 1) elimination of the flange which trapped keratinous debris at the margin of the system and promoted wide sinus formation: 2) elimination of the deeper conduit to facilitate fabrication and implantation since this portion of the device was not part of our primary evaluation objective: 3) limitation of the PTFE to the horizontal and only a small portion of the vertical part of the PETS terminal since the sinus invariably reaches the radius and horizontal portions of the system, and because forming the PTFE on the more vertical portion of the system produces pore distortion during fabrication. Extensive evaluation of available porous materials in vivo encouraged us to continue utilizing PTFE and Dacron velour. However, these experiments suggested that PTFE in a 15:1 expansion ratio (Impra, Inc.) would provide better tissue penetration and adhesion than the standard PTFE in a 5:1 expansion ratio (Gortex) and that carbon impregnated PTFE in a 15:1 expansion ratio (Impra) would be superior to PTFE without carbon. Furthermore, evaluation of various methods of rewetting the PTFE at the time of implantation demonstrated that saline introduced under vacuum was as effective as other methods, and did indeed improve tissue adhesion to PTFE. SEM studies demonstrated forming the PTFE in a flared configuration produced less pore distortion. Evaluation of various materials for the skirt demonstrated the superiority of Dacron velour in achieving exceptional tissue bonding and the ability to lessen the extensive chronic granulomatous reaction to Dacron by chemical stripping.

BEST COPY AVAILABLE

Histopathologic evaluation of all electively removed systems has demonstrated that by six months, the sinus reaches the Dacron velour. However, the delay in sinus progression caused by the PTFE-tissue seal, which is broken down either biochemically or mechanically over time, allows the connective tissue at the Dacron to mature. At six months, the connective tissue appears indistinguishable from dermis and the inflammatory reaction about the Dacron has subsided. We believe this "neo-dermis" provides the same inhibition to epidermal migration as normal dermis.

Changes in protocol which have improved our animal models and management have included 1) utilizing only miniature pigs which are >40 kg. in weight to ensure adequate growth and development, 2) inclusion of a minimal Tetracycline dose in the feed as prophylaxis against Group C/E hemolytic-streptococcus which have extreme wound virulence in pigs, 3) implantation of the skirt immediately under the dermis utilizing ipsilateral implantation which gives the animal a pain-free side in the early postoperative period and appears to minimize early trauma to the PETS implantation, 5) utilizing a dorsal implantation site which has provided us with better PETS implant longevity which is statistically significant when compared to other sites, 6) bacteriologic monitoring with swab cultures and antibiotic treatment based on sensitivities when two consecutive cultures are positive ($>10^3$ col/swab).

Table 1. shows our data with the PETS-2A-system implanted and monitored in standard fashion.

Table 1

	Series 1A Gortex 5:1	Series 1B Impra 15:1	Series 1C Impra 15:1 with Carbon	Series 1C tethered
1.	365 E	523 - 0	446 - 0	215 0
2.	365 E	523 - 0	446 - 0	215 0
3.	371 E	525 - 0	434 - I	201 0
4.	371 E	525 - I	434 - I	201 0
5.	345 I	244 - I	334 - I	173 0
6.	287 I	154 - I	301 - I	173 0
7.				166 0
8.				126 I
9.				49 T I
10.				49 T I

* 0 - Days Ongoing
E - Elective explant
T - Trauma
I - Explanted because of infection
As of August 20, 1984.

BEST COPY AVAILABLE

We believe the longevities achieved with this system in an unfriendly host are significant. In every instance, the infections necessitating explant of the systems with the more-expanded PTFE have occurred in association with detachment of the PTFE from the prosthesis. When the infection has been limited, it has been adjacent to an area where part of the PTFE has separated from the underlying urethane. We believe at the present time the PTFE - urethane bond weakens over time and that trauma initiates separation followed by infection. Further evaluation of this is underway.

We are convinced that this system will provide satisfactory performance in man for periods of two years.

Principal Investigator - Benedict D.T. Daly, Jr., M.D.
Co-investigators - Kurt A. Dasse, Warren Clay, Victor L. Poirier, Christian C. Haudenschild, Richard E. Fine, William J. Robinson, James N. Ross, Michael Szycher, Michael B. Worthington, Herbert L. Kayne, Michael B. Lewis, John Handrahan.

BEST COPY AVAILABLE

BLANK PAGE

Mechanical Circulatory Support

BEST COPY AVAILABLE

BLANK PAGE

UNIVERSITY OF WASHINGTON
(Cleveland Clinic Foundation)
(Whalen Biomedical, Inc.)
Development of a Thermal Ventricular Assist System (TVAS)
CONTRACT NUMBER: NO1-HV-28002

The objective of this continuing program at the University of Washington Joint Center for Graduate Study (JCGS) is to develop a permanently implantable Stirling/hydraulic power source to operate ventricular assist or full-heart replacement blood pumps. PVAD Model 12A and 12C blood pumps are being refined under subcontract to Whalen Biomedical, Inc. with in-vivo testing of System 7B and related work conducted by the Cleveland Clinic Foundation (CCF). The System 8 engine module, currently under development, is planned as the final preclinical design. Selective component fabrication of six System 8 engine modules was initiated and fabrication of two prototype versions was completed.

In-vitro and in-vivo tests are currently conducted with the integrated System 7B engine module and PVAD Model 12A blood pump. Computer modeling, mockup testing, and collaboration with the subcontractors for envelope configuration and implant location contribute to System 8 development. System, subsystem, and component operation in actual or simulated duty cycles are approaches used for life testing.

A 1-month in-vivo test was successfully conducted with the System 7B integrated package at CCF. The 286-lb male Holstein calf had an excellent recovery over the 30-day test period. The system demonstrated very good synchronized counterpulsation with the left ventricle. In-vivo tests were also successfully conducted to evaluate the permeation characteristics of a fluid-filled compliance chamber and to study the performance of a Model 12C PVAD pump with a new 0.75-mm thick diaphragm.

The design analysis in support of System 8 was completed. Many of the in-vivo detail drawings for engine, converter, and actuator components were completed. Engine and converter major components were fabricated and functionally tested. Two prototype engine modules are undergoing shakedown testing and performance evaluation. The design of the implantable System 8 actuator/controller is nearly complete and a prototype version has been fabricated. Cleveland Clinic has defined an engine and pump-actuator configuration for use in the human thorax which will eliminate the need for flexible hydraulic lines.

Life testing emphasizing Systems 6 and 7 critical components is continuing without failure. A complete System 7 integrated module is undergoing continuous in-vitro testing. A complete System 6 engine module with a metal diaphragm has operated continuously for over 1 year. Several bellows components have now exceeded 7 years of continuous testing representing nearly 6 billion cycles.

The current state of development provides a high level of confidence that the System 8 objectives to produce a clinically useful ventricular assist system with an 8-hour self-contained operating time for a 1-hour recharge time and a 10-year lifetime potential will be realized.

Maurice A. White, M.S., Principal Investigator (Project Director)
Yukihiko Nose', M.D., Ph.D., Principal Investigator (CCF)
Robert L. Whalen, S.B., Principal Investigator (Whalen Biomedical, Inc.)

BEST COPY AVAILABLE

NIMBUS, INC. and
CLEVELAND CLINIC FOUNDATION
DEPARTMENT OF ARTIFICIAL ORGANS
Thermal Ventricular Assist System
Contract Number NO1-HV-28001

This program is being conducted by Nimbus, Inc. in association with the Cleveland Clinic Foundation (CCF). The objective of this program is to develop a fully-implantable, thermally-powered, left ventricular assist system.

The basic system consists of a modified Stirling cycle engine, pnuematic controls and actuator, variable volume device, thermal management system, energy transmission system, and the CCF intrathoracic blood pump. Engine heat is developed by an electrically powered resistance heater. The heater is periodically energized and used to melt a volume of flouride salt. The heat of fusion stored in the salt volume provides a thermal battery capable of powering the assist system for up to eight hours. The periodic transfer of electrical energy across the skin is accomplished using inductive coupling. Thus with this system, patients are supported by a totally implanted device which can be free of any external power source for a considerable period of time.

Currently two thermal systems are being built-up and checked out for in vivo testing using CCF blood pumps. Both systems use engines which are heated continuously by electrical power. One system is a two module configuration comprised of an engine connected by flexible lines to a blood pump module which includes the pneumatic controls and actuator. The particular engine used for the two module system is a Mk 8, an earlier engine configuration. The latest engine design, the Mk 9 configuration is used in the second thermal system. With this engine, which is considerably smaller than the Mk 8, it is possible to mount the engine with the blood pump module, resulting in a single integrated configuration.

Detailed design of a prototype thermal salt system is in progress. This system uses a Mk 9 engine contained in a salt volume section. These are integrated into one module which is coupled by flexible lines to a blood pump-actuator controller module. In a human, such a system configuration would be accommodated by placing the blood pump module in its usual intrathoracic location and locating the engine module in the abdomen.

Supporting studies were continued on endurance testing of thermal system components. Early model engines are being run, providing data on bearing and reverser system wear. Actuator gas seals and bearings are being tested in special test fixtures, and a complete Mk 8 driven system is being run. Finally, component tests of the blood pump and variable volume device were conducted in vivo in calves.

J.C. Moise, Ph.D., Principal Investigator - Nimbus, Inc.
Y. Nose', M.D., Ph.D., Coinvestigator - Cleveland Clinic Foundation
A.L. Blubaugh, Ph.D., Engineering Manager - Nimbus, Inc.

BEST COPY AVAILABLE

TEXAS HEART INSTITUTE OF ST. LUKE'S EPISCOPAL AND TEXAS CHILDREN'S HOSPITALS
(Gould Incorporated and Thermedics Incorporated)
Development of an Implantable, Electrically-Actuated Heart Assist System
CONTRACT NUMBER: NO1-HV-02915

A permanent, implantable, electrically-powered ventricular assist system (THI/Gould VAS) has been developed for ultimate clinical use in patients with end-stage cardiac failure. The system includes five major integrated components: 1) pusher-plate blood pump; 2) electrical-mechanical energy converter; 3) implantable control/power module; 4) volume compensation compliance chamber; and, 5) external power supply/monitoring unit. All components of the system have been finalized and a complete operational THI/Gould VAS has been fabricated and tested. Maximum blood pump and energy converter life tests now exceed 6.6 and 3.4 years (results include: blood pump, five tests > 4 years; and, actuator, two tests > 2 years). The hybrid microprocessor-based control electronics have been reliable during in-vivo operation and are responsive to varying physiologic demands. In-vivo evaluations of thoracically-implanted volume compensation compliance chambers have demonstrated satisfactory performance and minimal tissue encapsulation. In-vitro tests of the internal rechargeable battery module have demonstrated discharge times and cycle life greater than 30 minutes and 2 years, respectively. Similar tests of the external battery unit yielded discharge times and cycle life greater than 10 hours and 1 year.

STUDY PERIOD	DURATION (Days) mean ± SD	RANGE (Days)
Short-term (n=9) < 1 month	19 ± 8	10 - 30
Intermediate term (n=14) 1 - 3 months	60 ± 14	42 - 79
Long-term (n=6)† > 3 months	135 ± 37	95 - 181

† Includes studies of 181, 180, 131, 116, 108, and 95 days

During the past year, in-vivo studies included two evaluations of a redesigned short, rigid, inflow conduit with durations of 180 and 116 days. This modification, as predicted*, eliminated problems with occlusive inflow pannus formation. Maximum blood pump stroke volumes of 90 ml/B were obtained throughout both studies at rest (pump rate < 90 B/min) and exercise (pump rate up to 120 B/min with pump output of 10.6 L/min). Thus far, 29 chronic electrically-actuated system studies have been performed in calves for durations up to 6 months with a cumulative in-vivo experience of 5.0 animal years of testing (table). Taken together, these results demonstrate the potential of the THI/Gould VAS for long-term (> 2 years) mechanical circulatory support and indicate system readiness for preclinical validation.

*THI Proposal No. 29214, February 6, 1984, in response to RFP NHLBI-HV-84-1.

Co-Principal Investigators: O.H. Frazier, M.D. and J.A. Chambers
J.M. Fuqua, Jr. L.A. Davies W.C. Clay
S.R. Igo L.M. Mahler S.D. Buczak
M.G. McGee T.T. Yen G.J. Creager
G.E. Pool M.L. Gillichbauer S.M. Parnis
O.U.J. Okereke, M.D.

BEST COPY AVAILABLE

THERMEDICS, INC.

(Children's Hospital Medical Center)

DEVELOPMENT OF AN IMPLANTABLE, INTEGRATED

ELECTRICALLY-POWERED LEFT HEART ASSIST SYSTEM

CONTRACT #NO1-HV-02914

The program objective is the development and evaluation of a complete, electrically-driven VAS intended for chronic cardiovascular assist, together with peripheral support and energy storage means that will permit a quasi-normal life style.

The MK IV electrically-powered Ventricular Assist System comprises a fully integrated heart assist pump, driver, controller, synchronizer, backup energy source, and power conversion unit in two implantable modules. The system can be powered from an externally-worn energy source, either by a percutaneous lead or via high-frequency AC power, transmitted across the intact skin.

Central to the system is a low-speed torque motor that powers a pusher-plate assist pump at one cycle per revolution. After eject is completed, the pusher-plate is free to return toward the fill position at a rate governed solely by the rate of blood influx to the pump. This technique yields inherently high reliability because the moving parts are few (five) and operate at low speeds.

A unique feature of the MK IV system is its ability to respond instantly to changes in heart rate, which reduces the complexity of synchronous control circuitry. Weight and volume of the assist pump/driver are 0.87 kg and 405 cc. Its operating efficiency is above 30%.

The implantable controller subsystem contains control, synchronizer and power conversion electronic modules, surrounded by an annular ring of ten 450 ma-hr nickel-cadmium cells. The battery provides discharge time of 40 minutes at 8 L/min and 120 mmHg mean outlet pressure. The synchronizer and controller provide synchronous counterpulsation, if a verifiable systolic interval exists; pumping on "full" if the flow rate permits operation above a minimum beat rate; or temporary reversion to fixed rate in the presence of low flows and insufficient ventricular contractility. Weight and volume of the controller/battery unit are 0.36 kg and 160 cc.

The third implantable system element is a variable volume chamber, designed to be implanted in the pleural space. The

BEST COPY AVAILABLE

flexible portion of the VVD, solution cast as a trilaminate of Biomer with a central core of butyl rubber, is adhesively bonded to a rigid titanium backing plate. It is cast in the fully-distended position to allow the restorative force of the elastomer to assist pump filling. Operation of the device was verified in vivo during six active and passive animal experiments that extended for periods up to 300 days. Liquid transport across the elastomer was found to be nil; ballast gases that originally filled the passive chambers were replaced in a relatively short time by oxygen and nitrogen in atmospheric proportions.

In vitro testing of the completed MK IV VAS, including the variable volume device, has continued for most of this year (28×10^6 cycles) without incident or interruption, Component tests of the elstomer diaphragm have exceeded 9.5 cumulative years without failure. The longest running of these has achieved 111×10^6 cycles.

Five studies of the complete MK IV VAS were undertaken this year in calves, for a total of 174 experiment days. The longest study reached 77 days, with the final 29-day study powered by the Transcutaneous Energy Transmission System (TETS). Counterpulsatile phasing was repeatable and responsive over the observed range of heart rates(60 - 130 beats/min) with flows observed to 7 L/min.

System characterization is now routinely performed using a direct microprocessor link between the NHLBI circulatory loop and our main computer.

We believe that the MK IV VAS has met most if not all of the developmental goals specified by the NHLBI guidelines. It is compatible in size and weight with humans of moderate frame size; VAD anatomic fitting studies have been performed successfully in subjects as small as 60 kg. The pumping criterion of 10 L/min at 120 mmHg mean outlet pressure and 15 mmHg mean inlet pressure has been achieved, and long-term evaluation of the system in vivo is in progress.

David B. Gernes, Principal Investigator
William Bernhard, M.D., Co-principal Investigator

BEST COPY AVAILABLE

NIMBUS, INC. and
CLEVELAND CLINIC FOUNDATION
DEPARTMENT OF ARTIFICIAL ORGANS
Development of an Electrohydraulic
Driven Left Heart Assist System
Contract Number: NO1-HV-02911

A left heart assist system intended for patients requiring chronic cardiovascular support is being developed on this program. Relative to others the Nimbus/Cleveland Clinic E3C system is unique in that the central anatomical location for the implanted components is the thorax; there are no components in the abdomen, nor are there any diaphragmatic penetrations. Also distinctive is the electrohydraulic energy converter and the blood contacting surface of biolized gelatin coating.

This four year program, now completed, has made significant progress in achieving a useful clinical device. Early effort concentrated on development of the basic blood pump-energy converter unit. Later work emphasized development of the other implanted components and refinement of the blood pump-energy converter configuration to make it more accommodative to a broader range of patient anatomies. In particular, during this last year key accomplishments were made in the areas of energy transmission, variable volume management, and diagnostic monitoring.

A NHLBI supplied Transcutaneous Energy Transmission System (TETS) was adapted to drive the E3C energy converter and extensive in vitro tests of TETS driven E3C systems were conducted. Satisfactory power range and functional compatibility was demonstrated. A breadboard rectifier circuit suitable for hybridization was developed as part of this effort.

Hermetically sealed internal batteries consisting of Ni Cad cells contained in titanium housings were fabricated, and satisfactory capacity and performance was demonstrated in in vitro tests. Prototype wiring harnesses were fabricated using custom titanium connectors. Tests of connectors and cables submerged in 37°C saline are in progress. No trace of intrusion of water or ions is apparent after 3 months.

In vivo tests of gas filled flexing variable volume devices continue to demonstrate that diaphragm tissue encapsulation can be minimized by use of velour treatment of the diaphragm surface. Diffusion results obtained primarily in long term in vivo tests, indicate that transfer rates of high molecular weight ballasts gases may be higher than originally predicted. Further investigation of the diffusion properties of diaphragm materials is being pursued.

A diagnostic monitoring system using signal transmission across the skin by a dipole source was developed. With this concept, diagnostic signals from permanent implanted source electrodes are picked up by surface electrodes placed on the skin, similar to ECG monitoring. All aspects of this diagnostic monitoring system have been confirmed in both in vitro and in vivo tests.

Other key activities this last year involved development of the hybrid version of the main E3C power supply and controller circuit. Fabrication of the hybrid is now near completion and checkout will begin soon. Also, in vitro

BEST COPY AVAILABLE

endurance tests were continued, with the longest running system (an early E-2 configuration) surpassing 4.7 years of operation without failure. One E3C-1 system was placed on *in vitro* endurance testing.

The culmination of the development knowledge gained over the past four years is represented by the Nimbus/Cleveland Clinic E3C-2 system, the concept being carried forth into the next program. This program, already underway, involves extensive reliability testing of E3C-2 systems. Eighteen systems are being fabricated, 12 to be placed on *in vitro* testing for two years duration, and six to be used for *in vivo* tests. The basic goal of the reliability program is to validate the readiness of the E3C-2 system for initial clinical application in humans.

John Moise, Ph.D., Principal Investigator - Nimbus, Inc.
Yukihiko Nose', M.D., Ph.D., Co-Principal Investigator - CCF
Ray Kiraly, M.S., Engineering Manager - CCF
Luiz Fujimoto, M.D., Investigator - CCF
Leonard Golding, M.D., Investigator - CCF
Bill Smith, M.S., Investigator - CCF
Hiroaki Harasaki, M.D., Ph.D., Investigator - CCF
Jim Payne, B.S., Project Engineer - Nimbus, Inc.
Ken Butler, M.S., Project Engineer - Nimbus, Inc.

BEST COPY AVAILABLE

NOVACOR MEDICAL CORPORATION
(Department of Cardiovascular Surgery,
Stanford University Medical Center)
Development of an Implantable Left Heart Assist System
CONTRACT NUMBER: NO1-HV-02908

An implantable, permanent, Ventricular Assist System (VAS) suitable for long-term human use has been developed. This integrated system incorporates the balanced MK22D solenoid energy converter coupled to a Model IVA dual pusher-plate sac-type blood pump.

The MK22D is the final step in the evolution of the balanced solenoid energy converter. The solenoid consists of two identical armature structures that move symmetrically with no reaction torques, gyroscopic effects, or momentum transfer to the body. Titanium beam springs couple the armatures directly to the pump's pusher plates.

The Model IVA blood pump has a circular pump chamber with tangential valve conduits and a seamless polyether urethane sac symmetrically actuated by dual pusher plates. The trilaminar sac is composed of diffusion controlling butyl rubber sandwiched between two Biomer layers.

The integrated pump/converter has a mass of 695 gm and an overall volume of 400 cc. It has demonstrated synchronous operation at rates to 180 bpm, output to 11 L/min, and mean aortic pressures to 160 torr.

The VAS includes a single diaphragm-type variable volume compensator with a rigid housing supporting a Dacron-velour-covered trilaminar flexing membrane.

An implantable, microprocessor-based, electronic control and power (IECP) subsystem has been designed. Using hybrid packaging and three semicustom integrated circuits, the IECP dynamically responds to a wide range of physiologic conditions and controls solenoid closure through a unique feedback servo system. Power and communications are provided by the Belt Skin Transformer, and backup power is available from integral rechargeable NiCd batteries.

In vivo experiments were continued with the MK22D/IVA system. A successful transition was made from the bovine to the ovine, which allows long-term system evaluation in a mature animal model, with stable hemodynamics and the absence of accelerated calcification. The change in animal model has been highlighted by an ongoing experiment with a sustained pump output of 10 L/min and no evidence of inflow conduit (expanded PTFE) occlusion after five months of continuous synchronous operation.

P.M. Portner, Ph.D., PI
P.E. Oyer, M.D., Ph.D., PI/Subcontr
J.S. Jassawalla, M.S., Co-PI
J.S. Brugler, Ph.D., Co-PI
A.K. Ream, M.D., Co-PI/Subcontr
P.J. Miller, M.S.
H. Chen, M.S.
G.F. Green, Ph.D.
D.H. LaForge, B.S.
J. Lee, M.S.
N. Ramasamy, Ph.D.
M.G. Conley, B.S.
F.K. Beering, B.S.
M.E. Billingham, M.B., B.S.

BEST COPY AVAILABLE

SAINT LOUIS UNIVERSITY SCHOOL OF MEDICINE
Clinical Application of Ventricular Assist Devices
Contract #NO1-HV-12909

From February, 1982 to August 1984, a paracorporeal, pneumatic sac-type ventricular assist device (VAD) designed by Pierce and Donachy[1] and produced by Thoratec* was inserted in 22 patients (pts) aged 15-72 (mean 52.6) years for ventricular failure refractory to drugs and intra-aortic balloon pump (IABP). Twenty pts were unable to be weaned from cardiopulmonary bypass (CPB) and 2 pts deteriorated while awaiting cardiac transplantation. Ten pts received left VAD's; 5 pts received right VAD's with an IABP for left ventricular support; and 7 pts received both right and left VAD's. Atrial cannulation was used for VAD inflow in all cases and repeat sternotomy was used for VAD removal. Heparin was used only during the weaning period.

Peak VAD flows ranged from 1.55-3.03 (mean 2.24) L/min/m^2, and the perfusions lasted 3 hours to 12 days. Although all 20 of the postcardiotomy pts were weaned from CPB with the VAD, eight of them died in the operating room of severe bleeding and biventricular failure. The other 12 pts underwent VAD perfusion for 9 hours to 12 days, and 9 pts were weaned after 3-12 days. Seven patients, 3 with left VAD's, 2 with right VAD's and 2 with BIVAD's are long term survivors of 5-27 months. The 3 pts with BIVAD's who were weaned demonstrated right ventricular recovery earlier than left ventricular recovery. Biventricular failure was present in almost all pts. However, two pts with isolated left ventricular failure did well with only left VAD's and are long term survivors. Pts with biventricular failure who received biventricular support (either right VAD with IABP or BIVAD's) had a greater chance of being weaned (5/12) and surviving (4/12) than those who received only a left VAD (1/8).

Nuclear angiographic measurements of left ventricular volume (LV vol) and ejection fraction (LVEF) were performed during asynchronous pumping and during pump off periods. With the VAD on, LV vol decreased but mean aortic pressure increased and LVEF decreased. Thus, the reduction of preload was offset by an increased afterload, so that minimal LV decompression occurred. Although preoperative ventricular function did not correlate with outcome, perioperative myocardial infarction occurred much more commonly in postcardiotomy non-survivors (7/13) than in survivors (0/7).

Thrombus occured in 3 right VAD sacs used for 3,5 and 12 days. This was attributed to frequent cannula clamping, which was discontinued. Subsequently, a small thrombus was noted in a left VAD sac which was used for 8 days. There was no clinical necropsy evidence to suggest embolization from the device.

From these data, we conclude:

1. Profound RV and LV failure may resolve with a VAD which does not provide complete ventricular decompression.
2. Biventricular failure is common in VAD candidates.
3. When present, biventricular failure should be treated with biventricular support.
4. The injured RV recovers sooner than the injured LV.
5. Perioperative infarction is an important determinant of survival in postcardiotomy VAD patients.

* Thoratec, Inc, Berkeley, CA

BEST COPY AVAILABLE

6. VAD sac thrombosis is rare unless the cannulas are frequently clamped.
7. Bleeding remains a major problem in VAD patients.

REFERENCES:

(1) Donachy JH, Lanois DL, Rosenberg G, Prophet GA, Ferrari O and Pierce WS. Design and evaluation of a left ventricular assist device: The angle port pump. Chapter in Assisted Circulation. (ed F. Unger) Academic Press, New York, 1978.

BEST COPY AVAILABLE

PUBLICATIONS:

(1) McBride LR, Pennington DG, Swartz MT and Pierce WS. Left atrial-aortic perfusion with a ventricular assist device. ASAIO Abstracts 11:7, 1982.

(2) Pennington DG, McBride LR, Swartz MT, Bashiti H, Hahn J and Pierce WS. Left atrial-aortic perfusion with a ventricular assist device. Transactions American Society for Artificial Internal Organs 28, 1982.

(3) Pennington DG, Merjavy JP, Codd JE, Swartz MT and Willman VL. Temporary mechanical support of patients with profound ventricular failure. Chapter in Assisted Circulation Second Edition (ed F Unger) Academic Press, New York. To be published.

(4) Pennington DG, Codd JE, Merjavy JP, Swartz MT, Barner HB and Willman VL. The expanded use of ventricular support systems in patients with ventricular failure and as a bridge to cardiac transplantation. Heart Transplantation 3:1 38 November 1983.

(5) Williams GA, Kaintz R and Pennington DG. Effects of a ventricular assist device (VAD) on myocardial function. ASAIO Abstracts 11:15, 1982.

(6) Samuals LD, Ho JE, Pennington DG and Swartz MT. Radionuclide ventriculography in patients with ventricular assist devices. Abstract Society of Nuclear Medicine, 1982.

(7) Pennington DG, Merjavy JP, Swartz MT, Codd JE, Barner HB, Lagunoff D, Bashiti H, Kaiser GC and Willman VL. The importance of biventricular failure in patients with postoperative cardiogenic shock. Ann Thorac Surg (Submitted).

(8) Pennington DG, Samuals LD, Williams GA, Palmer D, Swartz MT, Codd JE, Merjavy JP, Lagunoff D and Joist HC. Experience with the Pierce-Donachy ventricular assist device in postcardiotomy patients with cardiogenic shock. World Journal of Surgery (Submitted).

(9) Joist JH, Vargo JJ, Swartz MT and Pennington DG. Hemostatic alterations associated with the case of ventricular assist devices in man. Abstracts American Heart Association, 1984.

(10) Pennington DG, Bernhard WF, Golding LR, Berger RL and Watson JT: Ventricular assist device salvage of cardiotomy patients - Long term follow-up. Abstracts American Heart Association, 1984.

D. Glenn Pennington, M.D., Principal Investigator
George Williams, M.D., Co-Investigator
Hind Bashiti, M.D., Co-Investigator
David Lagunoff, M.D., Co-Investigator
J Heinrich Joist, M.D., Co-Investigator
John P. Merjavy, M.D., Co-Investigator
Larry Samuals, M.D., Co-Investigator
Marc T. Swartz, Research Associate

BEST COPY AVAILABLE

THORATEC LABORATORIES CORPORATION
Fabrication of Cardiovascular Devices
CONTRACT NUMBER: NO1-HV-92906

The primary purpose of this contract is to supply clinical quality ventricular assist devices (VADs) to Devices and Technology Branch investigators for clinical application. Included in the devices fabricated during the past year are new VADs, refurbished VADs, and atrial, ventricular, and aortic cannulas of various configurations. In addition, accessories, such as tool sets and electrical leads, were fabricated as required.

The VAD consists of a smooth seamless pumping sac made of segmented polyurethane enclosed within a rigid polysulfone case. Two tilting disc valves control flow direction, and the pump is pneumatically actuated by an external drive console.

To date, clinical VADs supplied from this contract have been used to support the pulmonary and/or systemic circulations for up to 2 weeks in twenty-two patients with severe refractory left, right, or biventricular failure after cardiac surgery. The temporary use of this VAD has allowed ventricular function in seven of these patients to improve sufficiently for subsequent device removal and hospital discharge.

David J. Farrar, Ph.D., Principal Investigator

BEST COPY AVAILABLE

THE PENNSYLVANIA STATE UNIVERSITY
LEFT VENTRICULAR BYPASS FOR MYOCARDIAL INFARCTION
GRANT NUMBER: 2 RO1 HL 13426

PNEUMATIC ASSIST PUMP: CLINICAL STUDIES. During the past year, our group has had the opportunity to use the left ventricular assist pump (LVAD) of our design in two patients and biventricular support, with similar pumps, in one patient. Each of the three patients had been in the urgent or emergency surgical category. The first patient, 59 years old, had been in profound cardiogenic shock for eight hours when first seen. Emergency single bypass graft and LVAD insertion was performed. The poor condition of the patient prior to operation precluded survival. The second patient (31 years old) underwent emergency mitral valve replacement. Four hours later, the patient developed low cardiac output and was returned to the operating room. Biventricular support was required. Severe pulmonary hypertension, due to multiple chronic pulmonary emboli, prevented successful circulatory support. The third patient, 62 years old, developed left heart failure after urgent mitral valve replacement and five bypass grafts, and LVAD was inserted. Adequate circulatory support was provided for a few hours. However, profound right ventricular failure, related to severe pulmonary hypertension, prevented a satisfactory outcome.

During the past several years, a blood pump of our design has been used in clinical application in five other centers around the world with a number of successful applications reported.

MOTOR ASSIST PUMP: LABORATORY STUDIES. Refinement of the cam type assist system continues. A new single board digital control system has been tested in vitro and a new 150 gram lighter motor designed. Eight animals have received the closed system with implanted compliance chamber; the longest survivor lived 130 days and the mean survival time is 79 days. One animal is alive and well at 87 days (August 17, 1984). The last two experiments employed a reduced size (6"x6"x3/8") compliance chamber that functioned as well as the larger system.

Extensive in vitro evaluation of the smaller, lighter roller screw, drive assist system was conducted this year. These results with this system indicate potential performance and reliability improvements over the cam system.

BEST COPY AVAILABLE

In vitro testing of a portable battery system and transcutaneous energy transmission system (modified Thermedics design), suitable for use have been conducted with favorable results.

William S. Pierce, M.D., Principal Investigator
Gerson Rosenberg, Ph.D., Investigator
David B. Geselowitz, Ph.D., Investigator
Donald L. Landis, Research Associate
James H. Donachy, Research Assistant
Alan J. Snyder, Graduate Assistant, Biomedical Engineer
William J. White, V.M.D., Veterinarian
G. Allen Prophet, B.S., Research Assistant
Kay Holtzman, Animal Care Supervisor

BEST COPY AVAILABLE

THE PENNSYLVANIA STATE UNIVERSITY
DEVELOPMENT AND EVALUATION OF AN ARTIFICIAL HEART
GRANT NUMBER: 5RO1-HL-20356

Pneumatically powered artificial hearts in two sizes (110 ml stroke volume - calf model, 85 ml stroke volume - human model) are undergoing continued bench and animal evaluation. The use of filler-free silicone rubber coated inlet (atrial) connectors has eliminated pannus formation and extended animal survival. The survival time following artificial heart replacement in calves has now been extended to nine months. Problems limiting longer survival relate to sac calcification (most prominent in high flexion areas of the segmented polyurethane sac) and growth of the animal with inadequate blood flow per kg body wt. The amount of calcification appears to be less in calves on warfarin sodium and etidronate disodium.

A cardiac transplantation program has now been initiated at The Milton S. Hershey Medical Center of The Pennsylvania State University. The pneumatic artificial heart developed by our group is suitable and appropriate for use as a "bridge" for total circulatory support in certain patients awaiting transplantation. Preparations are now being made to obtain the appropriate approvals for interim circulatory support with the artificial heart.

The cam and roller screw electric motor driven total artificial hearts have both undergone continued <u>in vitro</u> testing. Each system has automatically controlled cardiac output and provided left-right balance. No implanted transducers are required since aortic pressure is derived from left systolic motor current and left atrial pressure from left pump fill time. Pump beat rate and stroke time division are both automatically adjusted to maintain physiological pressures and flows.

The cam system has been implanted in five chronic animals. The last three calves lived 222, 33 and 63 days respectively. The 222 day calf, "E.T." was automatically controlled without adjustment for the entire experiment. The next calf lived 33 days and was in excellent health when a Pyrolyte disk of a Bjork-Shiley convexo-concave valve fractured, thus terminating the experiment. We have since returned to using Delrin Bjork-Shiley convexo-concave valves which have never failed in any of our pumps. The last animal survived 63 days and was terminated when the head of a cam follower shaft fractured and locked the rotor.

BEST COPY AVAILABLE

The last two animals utilized a sealed system with a small (6"x4"x3/8") implanted compliance chamber. The chamber functioned well and did not affect control although one chamber did lose gas.

In vivo studies with the roller screw are planned for the near future.

William S.Pierce, M.D., Principal Investigator
David B.Geselowitz, Ph.D., Co-Investigator
Gerson Rosenberg, Ph.D., Senior Research Associate
Donald L.Landis, Research Associate
James H.Donachy, Research Assistant
Alan J.Snyder, Graduate Assistant, Biomedical Engineering
Thomas J.Cleary, Biomedical Engineer
William J.White, V.M.D., Veterinarian
Paul E. Beard, Fabrication Specialist
G.Allen Prophet, Research Assistant

BEST COPY AVAILABLE

CLEVELAND CLINIC FOUNDATION
Biventricular Assist and Replacement Studies
GRANT NUMBER: HL24286-06

The long range objective of this grant is to identify the simplest (and hence most reliable) approach for controlling a dual pusher plate type total Artificial Heart (TAH) that will at the same time respond adequately to submaximal exercise demands. Any method that depends on the explicit measurement of physiological variables (pressures, flows) has been eliminated in favor of algorithms that utilize the pump characteristics itself to indicate hemodynamic status. Within this subset the choices reduce to either the two ventricles operating at variable (but independent (IND) rates) or else the rate of one slaved to the rate of the other, beating either synchronously LMS or alternately, LMA. The approach for solving the problem has been to implement each of these control approaches (for 3 week intervals) on the same calf for implantation periods lasting up to six months. Comparisons were then made not only between between algorithms on the same calf, but also between calves.

Specifically, data from 3 calves operated in the IND mode for periods of two to three months was used as baseline information for a longer term calf (six months and ongoing) in which the LMA, LMS, and Fixed Rate (FR) modes were used alternately for 3 to 4 week intervals. Towards the end of each interval, a complete battery of tests; standard treadmill exercise, (1.5 mph for 15 min), progressive exercise to obtain anaerobic thresholds, (a .5 mph increase in speed every 3 minutes up to 3 mph maximum), drug tests (afterload increase and decrease), and volume loading was done. Although data from this recent 191+ day calf is still being collated, results indicate the LMA mode to be at least comparable to VR, and perhaps superior from the standpoint of protecting the left atrial pressure in acute situations. As in previous experiments, a left to right flow differential (averaging 10 to 15%) was found to exist.

Based on this data, a modified TAH has been designed, built, and tested up to 12 days in two calf experiments in which a fixed stroke volume difference (15 to 20%) was built into the device. Future experiments will concentrate on using this prosthesis for heavily monitored control mode studies similar to the previous 6+ month calf.

Yukihiko Nose, M.D., Ph.D., Principal Investigator
Hiroaki Harasaki, M.D., Ph.D., Co-investigator
Gordon Jacobs, MSEE, Co-investigator
Raymond Kiraly, MSME, Co-investigator
Ryohei Yozu, M.D., Co-investigator
William Smith, MSME, Project Engineer
Teriuchi Shimomitsu, M.D., Project Cardiologist

BEST COPY AVAILABLE

PACIFIC MEDICAL CENTER, SAN FRANCISCO
Right Heart Function with Left Heart Assist
GRANT NUMBER 5 R01 HL 27275-03

Right ventricular (RV) failure is a frequent (20%) complication associated with use of a left ventricular assist device (LVAD) for refractory cardiac failure after open heart surgery. Two potential detrimental effects of an LVAD on RV function are 1) reduced septal contribution to RV contraction due to left ventricular (LV) decompression and 2) augmented venous return from the LVAD producing volume overload of an already marginal RV. There are also potential beneficial effects which include 1) the maintenance of coronary perfusion pressure and 2) reduced pulmonary pressures due to lowered LV filling pressures. Recently we have been using ultrasonic and hemodynamic techniques to evaluate these effects and to study the interaction between LV unloading and RV function in surgical patients and laboratory animals.

The effect of LV unloading on LV and RV cross-sectional areas of patients before routine open heart surgery was examined using transesophageal 2D echocardiography (TEE). LV unloading via the vent cannula prior to full bypass produced a significant decrease in LV systolic and diastolic cross-sectional areas. RV systolic and diastolic areas and pulmonary artery pressure also decreased significantly, while RV fractional area change increased over control levels indicating an increase in ejection fraction. Data obtained from LVAD patients by TEE have shown similar decreases in LV and RV dimensions and an increase in RV fractional area change during LV assist.

In an animal model RV and LV septum-to-free wall dimensions were measured with ultrasonic crystals before and during LV unloading using a pulsatile LVAD while cardiac output and heart rate were held constant. During synchronous activation of the LVAD, LV septum-to-free wall dimensions were reduced in systole and diastole. RV dimensions, however, showed slight but significant increases which were probably due to a leftward septal shift, and RV pressure fell slightly. This implies a reduction in RV contractility because larger RV dimensions were required during LV unloading to produce the same stroke volume. The overall ability of the RV to eject a given stroke volume was not impaired because of a concomitant beneficial decrease in RV afterload during LV assist.

No evidence of RV failure was demonstrated during LV assist in any of our studies. In fact, the observed dimensional and hemodynamic effects of an LVAD imply a positive effect on the RV, especially in patients with passively elevated RV afterload secondary to increased LV filling pressures. The animal experiments, however, suggest that this effect will not be as pronounced in patients with less-diseased hearts. This hypothesis is supported by greater beneficial effects of LV unloading on RV function as previously found in patients with poor (<55%) versus relatively normal LV ejection fractions. Therefore, right heart performance will be determined by a balance between the state of the RV myocardium and the LVAD's beneficial and detrimental effects on preload, afterload, and contractility.

David J. Farrar, Ph.D.
Peter G. Compton, M.S.
James J. Hershon, M.D.
J. Donald Hill, M.D.

BEST COPY AVAILABLE

MONTREAL GENERAL HOSPITAL
Fluid dynamics in transparent natural blood vessels
GRANT NUMBER: 5 R01 HL 29502-02

To elucidate the possible connection between blood flow and the localization of atherosclerosis and thrombosis in large arteries of the mammalian circulation, we have studied the detailed flow patterns in the dog aorta using cinemicrographic techniques.

Isolated transparent arterial trees containing the heart and the ascending and descending aorta with their major branches were successfully prepared from dogs by fixing under physiological pressure, dehydrating with ethanol and finally suspending them in oil of wintergreen. Flow was visualized by taking 16 mm cine films of the motions of tracer polystyrene microspheres in dilute suspensions undergoing steady flow through the transparent natural vessels. In the aortic arch, it was found that complex spiral secondary flows and recirculation zones form at each branching site over a wide range of Reynolds numbers. Particles in the mainstream were deflected sideways at the flow divider and travelled laterally and some backward along the vessel wall, and then some entered the side branches, while others rejoined the mainflow in the descending aorta after describing spiral orbits. A recirculation zone was formed in each branch adjacent to the vessel wall opposite to the flow divider. When observations were made along the axis of the aorta, it was found that, looking down the aorta, the fluid revolved in a clockwise direction. Apparently, there was only one helicoidal flow rather than the two that had been anticipated. In vessels having an imperfectly opened aortic valve, it was also observed that strong eddies form at the entrance region of the aorta slightly downstream of the aortic sinus. In the descending aorta, paired thin layered spiral secondary flows, located symmetrically about the common median plane of the main and side branches, were formed at the T-junction of the celiac, cranial-mesenteric and right and left renal arteries.

Takeshi Karino, Ph.D., Principal Investigator
Hitoshi Kinomoto, M.D., Postdoctoral Research Fellow
Yasunori Sohara, M.D., Postdoctoral Research Fellow

BEST COPY AVAILABLE

UNIVERSITY OF UTAH
LVAD and RVAD with Portable Electropneumatic Drive
GRANT NO. 1-R01-HL-29751

Comprehensive development of implantable left and right ventricular assist devices intended for long-term application has begun. The LVADs and RVADs are pneumatically powered by the Utah Heart Driver or Heimes Portable Heart Driver, thus permitting assist device use away from the hospital following recovery from the implantation procedure. The assist devices are placed orthotopically within the chest with the drive lines exiting via the abdominal wall. A specially designed inflow cannula will be inserted through the atrial appendage. Assist device outflow will be pumped through a woven Dacron graft anastomosed to the corresponding great vessel. The development program includes device manufacturing and many aspects of performance evaluation.

The right and left ventricular assist devices are made from thermoplastic polyurethane. All components can be made using the vacuum forming process. The seamless ventricular intima is made either by vacuum forming or solution casting. Although originally designed to use commercial tilting disc prosthetic valves, the blood pumps can be easily modified to accept vacuum formed monocusp valves manufactured in our laboratory. Use of these materials and manufacturing processes minimizes the cost and time for blood pump production.

The LVADs and RVADs will be evaluated by durability testing, pumping performance characterization, and in vivo implantation. Durability testing includes pumping of air diaphragms and assist devices without valves in pressurized chambers. Complete assist devices are also continuously pumped on simple mock circulation systems. Pumping performance analysis will be made with a mock circulation instrumented to measure blood pump pressures and flows as the ventricular assist device pumps by itself or in parallel with a normal or failing artificial ventricle. Animal implant studies will evaluate the LVADs and RVADs during single and bi-ventricular support of normal and failing sheep hearts. Some studies will be long-term survival while others will have device removal several weeks after implantation. All experimental animals will undergo rigorous hemodynamic and hematologic evaluation before, during and after ventricular assist device application.

Willem J. Kolff, M.D., Ph.D., Principal Investigator
George M. Pantalos, Ph.D., Co-Principal Investigator
Donald B. Olsen, D.V.M., Co-Principal Investigator
William C. DeVries, M.D., Co-Principal Investigator

BEST COPY AVAILABLE

CLEVELAND CLINIC FOUNDATION
Compliance System for Implantable Blood Pumps
GRANT NUMBER: 1-R01-HL 30426-02

Every pulsatile blood pump has a volume change behind the diaphragm or pusher plate equal to that on the blood side of the diaphragm. With the integration of implantable electrical and thermal drive systems with blood pumps, methods to accommodate this variable volume must be developed.

A gas-filled intrathoracic compliance chamber is a simple and practical solution to the variable volume problem. The prerequisites for this system to work properly are 1) biological compatibility which would allow stable and acceptable pressure-volume characteristics for long duration, and 2) retention of the gas mixture in an environment in which gas diffusion gradients inherently exist.

As previously reported, lenticular shaped, dacron velour covered polyurethane compliance chambers showed stable, thin compliant tissue capsule formation in calves in durations of up to two years. These good results were reproduced in experiments in which the polyurethane membrane was replaced by Hexsyn which offered fabrication advantages. In addition, dynamic testing showed that energy consumption due to inflation and deflation work was quite low at volume flow rates over the range from 180 to 500 ml/sec. Therefore, the biological compatibility can be considered well established.

Permeability testing showed that sulfur hexafluoride, a non-toxic, medically-used gas, would have slow permeation rates and serve well as a buffer gas in the compliance gas mixture. In vivo experiments currently underway are being used to quantify the concentrations of the physiologic gases for equilibrium conditions in a closed system and gas diffusion rates. For these studies sealed, non functioning compliance chambers are implanted in the thorax of calves. Chambers which were initially air filled show faster rates of volume loss than chambers initially filled with the SF_6-buffered gas mixture.

Integrated blood pump-compliance chamber in vivo experiments were initiated in which the systems were implanted as a sealed unit without external pressure or sample taps. Compliance gas volume is monitored by a Hall-effect sensor on the compliance chamber. These experiments are demonstrating that buffer gas diffusion, although relatively low, is substantial enough to necessitate some gas addition for long term implants. Accordingly we are now studying buffer gas make-up methods including constant rate as well automatic on-demand types.

Yukihiko Nose, M.D., Ph.D., Principal Investigator
Raymond J. Kiraly, M.S., M.E., Co-Investigator
Hiroaki Harasaki, M.D., Ph.D., Co-Investigator
William A. Smith, M.S., M.E., Project Engineer
Satoru Kaneko, M.D., Fellow

BEST COPY AVAILABLE

UTAH BIOMEDICAL TEST LABORATORY INC. (UBTL)
Myocardial Recovery After Acute Ischemic Heart Failure
GRANT NUMBER: 1 R01 HL 33805-01

We have previously demonstrated that prolonged ventricular fibrillation in the extracorporeally-supported sheep will result in severe subendocardial damage and a total loss of pumping ability (the "stunned myocardium"). This model for acute ischemic heart failure when supported with biventricular bypass results in eventual recovery and restoration of tolerable cardiac hemodynamics.

We are presently developing techniques to correlate myocardial metabolism with hemodynamic function during the injury period and the transition to recovery. Current efforts in the first month of this research grant have resulted in the development of myocardial biopsy techniques, delineation of pathologic and biochemical methodologies, improvements in our biventricular support system, and cardiac function monitoring.

Jeffrey L. Peters, Ph.D., M.D., Principal Investigator
Clifford S. Kwan-Gett, M.D., Co-Principal Investigator
Kelly W. Smith, E.E., M.D., Co-Principal Investigator
Gregory J. Wilson, M.D., Co-Principal Investigator
Donald A. Mickle, M.Sc., M.D., Co-Investigator
Alexander D. Romaschin, Ph.D., Co-Investigator
Barry L. Bagley, B.A., Collaborating Scientist
L. Steven Beck, D.V.M., M.S., Collaborating Scientist
John A. Burkart, Ph.D., Collaborating Scientist
Therese A. Davy, B.Sc., Collaborating Scientist
George Jackowski, Ph.D., Collaborating Scientist
Karla Kornmayer, M.D., Collaborating Scientist
David L. Mock, M.D., Collaborating Scientist
Clyde Null, M.D., Collaborating Scientist
George F. Rich, M.E., M.E.B.E., Collaborating Scientist
Gary R. Snider, M.D., Collaborating Scientist
Elizabeth Sonne, B.Sc., Collaborating Scientist
Floyd Sweat, Ph.D., Collaborating Scientist

BEST COPY AVAILABLE

*Thermedics Inc. and Childrens Hospital Medical Center

Device Readiness Testing of Implantable
Ventricular Assist Systems

Contract # N01-HV-48070

The objective of this program is the establishment of the reliability and operating characteristics of the Thermedics ventricular assist system. The data generated as a result of this program will be used to support an application for an investigational devices exemption. The system to be tested will be based around the Thermedics MK-IV energy converter. This converter is powered by a low speed torque motor, has a minimum of moving parts, and is assembled as an integrated unit with the Thermedics model 14 pusher plate pump. This ventricular assist device is coupled with an implantable battery pack and controller unit, a variable volume device, and a transcutaneous energy transmission system to create a totally implantable ventricular assist system that requires no penetration of the skin. An external battery pack and electronic components are also part of the system.

This program is now in the first stage. Primary emphasis has been on development of suitable test protocols and the establishment of manufacturing and acceptance specifications. Development of test protocols is a cooperative effort between the contractors involved in the project, the program office, and an independant review board. These protocols will apply to all invitro and invivo characterization and reliability testing.

Manufacturing and acceptance specifications are being established such that the devices will be fabricated in accordance with good manufacturing practice. Manufacture of the devices has begun.

Warren Clay, Principle Investigator
William Bernhard, M.D. Co Principle Investigator

BEST COPY AVAILABLE

ABIOMED (APPLIED BIOMEDICAL CORPORATION)
MASSACHUSETTS GENERAL HOSPITAL
CHARLES STARK DRAPER LABORATORY
Device Readiness Testing of An Electrohydraulic Ventricular Assist System
NIH-NO1-HV-48073

The overall objective of this three year program is the demonstration of the Clinical Readiness of an Implantable Electrohydraulic Ventricular Assist System (VAS). Potential recipients of such a permanent device are patients with end-stage ischemic or idiopathic cardiomyopathy.

During the past four years, the ABIOMED VAS progressed from the conceptual stage to a final prototype with demonstrated effectiveness, both in vitro and in vivo. During the next three years, a number of systems will be fabricated and subjected to continuous in vitro reliability testing under simulated physiological conditions with the specific goal of attaining a two-year operational life-time. Concurrently, studies will be performed to achieve 25 animal-months of in vivo experience with a mean duration of approximately five months.

The system to be tested consists of (1) a dual-chambered, seamless blood pump with trileaflet valves, fabricated using Angioflex®, a polyether-urethane, as the blood contacting material; (2) an electrohydraulic energy converter encased in titanium housing with an axial flow pump and a fluid-shuttling two-position four-way sleeve valve; (3) an internal rechargeable 10 cell NiCd battery pack with an operational capacity of 30 minutes; (4) an internal electronic controller based on RCA 1805-A microprocessor; (5) an external monitor pack; (6) a rechargeable external AgZn power pack capable of 10 hr operation; and (7) a Thermedics transcutaneous energy transmission device.

During the first year of this program, 16 to 20 complete devices will be fabricated according to defined protocols. Twelve systems will be used in the reliability testing, while at least four of the remaining systems will be used for animal experiments. All subcomponents and subsystems will undergo QC/QA and acceptance testing to select qualified components for assembly. All assembled systems will be subjected to a burn-in period to weed out system infant mortality prior to the initiation of life-testing and implantation. Identical systems will be used in the in-vitro testing and in-vivo implants, without the use of substitution components. Percutaneous connections will be used until experience is gained on the transcutaneous system.

Anatomic fit studies will be conducted on cadavers to determine device placement and orientation, organ and tissue compression effects, anastomotic site, and apical insertion technique.

In vitro reliability testing will be initiated approximately nine to twelve months into the program and will continue for two years. Chronic experiments are scheduled to start in the second year. Prior to reliability testing and in vivo studies, each qualified system will undergo an extensive in vitro characterization with and without a mock loop to map out its steady state characteristics and transient response. A range of filling and outflow pressures with the associated flows and

BEST COPY AVAILABLE

power consumption will be documented. System tracking of conditional changes, such as beat rate, synchronization, filling, and outflow pressure changes will be recorded. This set of data will serve as a reference for in vitro evaluation to determine performance changes subsequent to device explant or at the end of the reliability test period.

Reliability testing will be performed in a temperature (37 C) controlled saline loop and bath, with a common inflow plenum and adjustable filling pressure, up to a maximum of 20 mmHg. Each device outflow pressure is set through adjustable fluid level column height. Flow is monitored using a venturi. Filling and outflow pressures, flow and device power consumption are monitored once per hour. In addition to scheduled sampling, threshold level detectors are used to initiate data monitoring and recording in the event a device flow falls below the predefined level of 4 lit./min, the NHLBI criterion for system failure.

Chronic experiments will be divided into two groups, each operating respectively in the copulsating or the counterpulsating mode. The ABIOMED system lends itself to operation in both of these modes. The rationale is to determine whether long term physiological or pathological differences exist for the two different modes of operation.

Acute in vivo system characterization will be performed during the early phase of the program in both the single and the biventricular assist modes. With minor change in the configuration, the system can provide support to both ventricles with no change in the drive and control unit, nor the system size and weight. This mode of operation can address the patient population in which chronic single ventricular support may not be sufficient.

Project Director: R.T.V. Kung, Ph.D.
Principal Investigators: P.I. Singh, Ph.D. and D.M. Lederman, Ph.D.
ABIOMED, Senior Investigators
B.B. Adams, B.S., Mechanical Engineering
W.J. Bolt, B.S., Electrical Engineering
R.D. Cumming, Animal Studies; Consultant: N.K. Harpster, D.V.M.
T.E. Moutafis, B.S., Mechanical Engineering
J. Snow, B.S., Test and Measurements
C.L. Strohl, B.S., Plastics Engineering
CHARLES STARK DRAPER LABORATORY, P.I.: R. Gardner, B.S.
B. Beaton, B.S., Quality Control
R.G. Butler, B.S., Control
F. Petkunas, M.S., Electronics Fabrication
F.E. Sevier, B.S., Power Sources
MASSACHUSETTS GENERAL HOSPITAL, P.I.: M.J. Buckley, M.D.
W.G. Austen, M.D., Surgery
P. Block, M.D., Cardiology
L. Ellman, M.D., Hematology
J. Fallon, M.D., Pathology
D.M. Philbin, M.D., Anesthesia
W.J. Powell, M.D., Physiology
A. Schiller, M.D., Anatomic Fit Studies

BEST COPY AVAILABLE

BLANK PAGE

Ultrasound B-Scan Assessment Program

BEST COPY AVAILABLE

BLANK PAGE

RESEARCH TRIANGLE INSTITUTE
Data Coordinating Center for the
Ultrasound B-scan Imaging Assessment Program
CONTRACT NUMBER: NO1 HV 12917

The Ultrasound B-scan Imaging Assessment Program has consisted of a planning phase, a pilot study, a main study, and is currently in the process of a follow-up study. The purpose of the work is to assess the capabilities of ultrasound B-scan in imaging atherosclerotic lesions in carotid and iliofemoral arteries. B-scan is compared with results of angiography and with pathology of endarterectomy specimens. In addition to the inter-technique evaluation of the capability of B-scan for detection and quantification of atherosclerotic lesions, an intra-technique evaluation of the repeatability and variability of each of the techniques, B-scan, angiography, and pathology, has been undertaken. During the course of the main program which ended enrollment as of the end of March 1984, over 1,200 individuals were enrolled. Of these, approximately 1,100 were entered into the inter-modality evaluation and the remainder (randomly selected) into the intra-modality study.

Preliminary results indicate that dimensions as measured by B-scan tend to be somewhat larger (e.g., 0.5 mm for the minimum residual lumen) than those measured by angiography. However, the coefficient of variation for the two techniques as determined by intra-modality analysis of repeatability and variability are of the same order of magnitude. Inter-modality comparisons of B-scan as compared with angiography indicates a 95 percent sensitivity for detection of severe carotid artery disease and an 81 percent sensitivity for detection of mild to moderate disease. The overall sensitivity of B-scan as compared with angiography is 87 percent.

Analyses of the final data base, including comparisons of B-scan, angiography, and pathology continue.

Fred A. Bryan, Jr., Ph.D., Project Director
A. Vijaya Rao, Ph.D., Deputy Project Director

BEST COPY AVAILABLE

THOMAS JEFFERSON UNIVERSITY HOSPITAL
Ultrasound B-Scan Assessment Program
CONTRACT NUMBER: NO1 HV 12912-02

In April 1981, the Division of Ultrasound and Radiologic Imaging, Thomas Jefferson University and Medical College and four other medical facilities received a three year contract from the National Institute of Health, Division of Heart, Lung and Blood Institutes to determine the efficacy of B-Scan imaging in the detection of atherosclerotic plaques in both the carotid and lower extremity arteries. Patients participating in the B-Scan study had had recent arteriographic studies of the carotid and lower extremity arteries. Staff physicians from the Division of Ultrasound and the Department of Radiology examined the respective studies and completed protocol sheets in a double-blind study. The data sheets were designed so that measurements of the plaque that produced the minimal residual lumen of the carotid arteries were accurately calculated. The cases were read for reliability and variability or for specificity and sensitivity. The completed protocol sheets and the completed sheets for physical examination, medical history and functional studies were forwarded to the Research Triangle Institute for statistical analysis. Any specimen retrieved in an intact state during a carotid endarterectomy was processed by the pathologist according to protocol in order to confirm these findings. Similarly, the arteries of the lower extremity were studied. However, the specimens were not studied from a pathology standpoint. Approximately 1000 cases were evaluated during the contract period by the participating facilities. These institutions met quarterly to review any ongoing or newly encountered issues relating to the study. The personnel of Thomas Jefferson University Hospital examined 198 carotid patients and 36 lower extremity studies. The end results of this study indicates that there may be a role for B-Scan ultrasonography in the diagnostic evaluation of atherosclerotic plaques of the carotid and lower extremity arteries. An extension to the initial contract was awarded January 1983 for a follow-up examination of only the carotid patients. This examination, currently in operation involves inviting patients back for a follow-up examination 12-18 months after their initial study. This will make it possible to ascertain progression or regression of atherosclerotic plaques on asymptomatic patients who have not had surgical intervention. Fifty-four patients have been enrolled in the follow-up study to date. Patient followups are being performed in a double-blind study and all pertinent information is forwarded to the Research Triangle Institute for statistical analysis. A new contract proposal has been submitted recently for a second follow-up examination 36 months post-initial examination. In addition to the B-Scan and its functional studies, a limited history and physical examination as well as a lipid profile will be carried out. This should provide full insight into the adequacy of B-Scan imaging and complementary functional studies.

Barry B. Goldberg, M. D., Principal Investigator
Stanton N. Smullens, M. D., Co-Investigator

BEST COPY AVAILABLE

Diagnostic Instrumentation

BEST COPY AVAILABLE

BLANK PAGE

BEST COPY AVAILABLE

JET PROPULSION LABORATORY, CALIFORNIA INSTITUTE OF TECHNOLOGY
Computer Enhancement of Intravenous Coronary Angiograms
GRANT NUMBER: 5 ROI HL 30010-03

Under optimum exposure conditions, coronary arteries can frequently be faintly seen on intravenous angiograms but not with sufficient clarity for diagnostic use. Computer processing methods are being developed as part of this study to improve visualization of these images. A complex combination of spatial and temporal filters initially developed to enhance the arterial shadows has been replaced by a simpler and faster single frame processing technique based on a feature-dependent high-pass filter. Results to date on both animal and human angiograms indicate that substantial improvement in image quality can be achieved by the processing algorithms but that overall quality is not yet sufficient for diagnostic use.

Robert H. Selzer, M.A., M.S., Principal Investigator
David H. Blankenhorn, M.D., Collaborating Investigator
Donald W. Crawford, M.D., Collaborating Investigator.

BEST COPY AVAILABLE

UNIVERSITY OF UTAH
Temporal Filtration Fluoroscopy, Tomography and 3D Display
GRANT No. R01 HL 30001

Diagnostic quality digital coronary angiograms have been obtained and analyzed in comparison to simultaneously obtained cine angiograms using the Thomson CSF Broadcast 9300 video filtration device. Technical details of the method have been reported (Hardin, et al. Radiology 151(2):517-520, May, 1984). Analysis of comparative cine and digital stenotic segments shows only moderately good correlation, partly due to y-axis resolution problems caused by interleaved video readout. Efforts are underway to obtain progressive video readout to improve the video images, and a clinical protocol has been approved to evaluate the video highpass filtration technique using 4-4.5 French coronary catheters and dilute contrast material. Our ultimate goal is to develop a system suitable for outpatient screening.

Use of a Lexan plug model in vivo has shown that neither the digital nor the cine assessment of known stenoses is particularly accurate. In an effort to improve quantitative performance we have designed and manufactured a coronary stenosis phantom which should allow better experimental assessment of stenoses with the resultant ability to fine tune a system for more satisfactory in vivo performance.

Work on cardiac tomography continues under the direction of Robert A. Kruger, Ph.D. (see separate abstract).

3-D display on a vibrating mirror system has been analyzed in comparison wih 2-D display of identical phantom data. Feasibility of using this display system for viewing deblurred tomographic slices of other phantoms and in vivo tomograms is being studied.

James A. Nelson, M.D., Principal Investigator
Robert A. Kruger, Ph.D., Co-Principal Investigator
Bruce E. Bray, M.D., Co-Investigator
Frederick L. Anderson, M.D., Co-Investigator
William H. Barry, M.D., Co-Investigator
Brent S. Baxter, Ph.D., Co-Investigator

BEST COPY AVAILABLE

UNIVERSITY OF IOWA
Image Processing of Coronary Arteriograms
GRANT NUMBER: 1 R01 HL 29976-03

We have shown that the estimation of the severity of coronary atherosclerotic stenosis by the assessment of percent diameter reduction is a poor predictor of the physiological significance of the coronary lesion. One of the major goals of our research on this grant is to develop and test methods of analysis of standard coronary arteriograms which will more accurately predict the functional significance of individual coronary lesions in humans. We previously reported that computer-assisted videodensitometry (VID) yields information which correlates with the minimal cross-sectional area of the stenotic coronary lumen and which also correlates with the physiological significance of the coronary lesion.

In the present study, we examined two methods of VID background subtraction, evaluated the reproducibility of VID, and compared the results of VID to independent geometric and physiological variables. To accomplish these goals, two sequential cineangiographic frames of proximal left anterior descending coronary arteries from 17 patients were digitized. Normal and diseased segments and adjacent background regions were chosen by two observers in each angiographic frame. Background subtraction was accomplished using two different procedures. Integrated gray level (GL) and optical density (OD) of the narrowest part of the coronary artery were then determined. The GL and OD of each lesion, as well as the percent stenosis (estimated from the digitized images) were each compared to the minimal lumen area obtained by quantitative coronary angiography (QCA) and to a measure of the functional significance of the coronary obstruction. Functional significance of each obstruction was measured by intraoperative Doppler reactive hyperemia studies of the peak-to-resting velocity ratio (PRVR) after a 20-second left anterior descending coronary occlusion.

Results:

	% Stenosis	OD	GL
PRVR	r = -.24	r = .78	r = .79
QCA	r = -.43	r = .82	r = .80

The particular method of background subtraction did not effect the results of our experiment. Reproducibility of VID analysis from frame to frame was excellent (r=.90 for OD; r=.96 for GL), and interobserver reproducibility was also good (r=.87 for OD; r=.89 for GL). Estimation of % stenosis did not correlate well with QCA or PRVR. Thus, computer-assisted videodensitometry of coronary lesions allows rapid and accurate estimation of lesion geometry and functional significance. We are currently continuing our investigations with coronary videodensitometry and other computer analytic methods in the analysis of coronary arteriograms of humans.

Melvin L. Marcus, M.D., Principal Investigator
David J. Skorton, M.D., Co-Principal Investigator
Steve M. Collins, Ph.D., Co-Investigator
David G. Harrison, M.D., Co-Investigator
Carl W. White, M.D., Co-Investigator
Loren F. Hiratzka, M.D., Co-Investigator

(Maryl R. Johnson, M.D. is now a co-investigator on this project. Elizabeth E. Ericksen, M.S.E.E., Steven R. Fleagle, B.S.E.E., and Philip Aylward, M.D. were collaborators on this particular experiment.)

BEST COPY AVAILABLE

UNIVERSITY OF PENNSYLVANIA
Visualization of Coronary Arteries and Bypass Grafts
5 R01 HL 29985-03

We are applying technologies which have arisen in computer science and psychophysics to the improvement and evaluation of clinical performance as related to coronary arteries and coronary bypass grafts. Specifically, we are investigating how images from intravenous digital subtraction angiography and from digital subtraction root arteriography can be enhanced, and comparing the efficacy for lesion detection and quantitation of the enhanced images with unenhanced images and with those obtained by selective coronary arteriography. The enhancement techniques include the use of standard image processing methods, and specifically developed techniques for vessel detection, three-dimensional blood-vessel reconstruction, modelling or myocardial dynamics, medial line representation, lumen size estimation, and display of vessel structure. Our theoretical ideas are being implemented into working software packages, which will then be evaluated by the techniques of Receiver Operating Characteristic (ROC) analysis applied to observer performance tests on images from a swine coronary atherosclerosis model.

Specifically, during the second year of this three year grant we have developed a package for automatic measurement of coronary vessels from digital angiograms and a mathematical model for computer generating masks for an arbitrary combination of cardiac and respiratory phases. A program appropriate for non-stationary histogram equalization of DSA images has been developed, implemented, and tested. The process of artifically inducing coronary arterial disease in swine has begun and such swine have been imaged. Equipment has been built and tested to monitor and record the respiratory and cardiac cycles and to correlate them to the imaging process.

Gabor T. Herman, Ph.D., Principal Investigator
Leon Axel, M.D., Ph.D., Co-Investigator
Harold Kundel, M.D., Co-Investigator
Robert LeVeen, M.D., Co-Investigator
Jayaram K. Udupa, Ph.D., Co-Investigator
Gerald Wolf, M.D., Co-Investigator

BEST COPY AVAILABLE

BOWMAN GRAY SCHOOL OF MEDICINE
RESEARCH, DEVELOPMENT AND EVALUATION OF SYSTEMS
FOR NONINVASIVE DETECTION AND QUANTIFICATION OF
ATHEROSCLEROTIC LESIONS
CONTRACT NO: NO1-HV-12902

The detection and quantification of early atherosclerosis can be accomplished by measuring the arterial distensibility and wall thickness changes. As wall thickness increases, the arterial distensibility decreases and the pressure-strain elastic modulus increases. Arterial distensibility is defined as the systolic diameter minus the diastolic diameter divided by the diastolic diameter, and the pressure strain elastic modulus is the pulse pressure divided by the distensibility.

The research approach included an non-human primate model, development of deconvolution procedures to improve axial resolution, and control of the transducer output pulse. The primate colony consisted of 18 adult male Macaca fascicularis monkeys divided into 3 groups. Group I (7 monkeys) were fed an atherogenic diet high in butter, group II (7 monkeys) were fed an atherogenic diet high in peanut oil, and group III (4 monkeys) were fed monkey chow as controls. Group I animals developed a mean plasma cholesterol concentrations of 607 $\pm$ 19(SD) mg/dl, group II mean plasma cholesterol concentration 435 $\pm$ 106 mg/dl, and group III mean plasma cholesterol concentration 118 $\pm$ 13 mg/dl. These animals were sacrificed and the results of histology will be presented.

To detect small changes in primate and human arterial wall thickness, deconvolution algorithms using the procedure of Papoulis and Chamzas were developed. Additions to this algorithm included tissue frequency dependent attenuation compensation and a variable threshold. Deconvolution results from young, healthy human common carotid artery echoes showed two distinct echo spikes. Results from echoes in patients with known atherosclerosis and participating in an exercise rehabilitation program showed layers in the .050 to .120 mm range.

Efforts to control the transducer output pulse were done with the EDO Corporation and later with NAMLAK. The procedure uses system identification algorithms to obtain a narrow output pulse. Results to date show a pulse with a main time lobe width of 200ns and time sidelobes greater than 15dB down. Axial resolution at 200ns corresponds to .077mm.

Ralph W. Barnes, Ph.D., Principal Investigator
M. Gene Bond, Ph.D., Investigator
David W. Griffith, Jr., Ph.D., Investigator
Ward A. Riley, Jr., Ph.D., Investigator

BEST COPY AVAILABLE

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
NMR Imaging of Human Coronary Arteries
CONTRACT NO. NO1-HV-38044

NMR imaging has clearly become established as a diagnostic clinical modality, and it is certain to become widely available. A major attraction of the technique is its totally non-invasive nature and the apparent lack of hazards for devices operated below FDA guidelines. This non-invasiveness extends to the visualization of vasculature, which becomes evident because the process leading to image formation by NMR is slow (the time scale being from 10 msec to 1sec) compared to flow processes.

In this program we address techniques for imaging the coronay arteries and for the display of vasculature. The NMR imaging process consists of the application of short signal-generating sequences at preset time intervals. The image is formed from a multiple set of such sequences, from 100 to 4,000. The interval between sequences can be governed by a trigger signal obtained from the heart, in this way becoming synchronized to the cardiac cycle. If desired, imaging can be stopped during certain phases of the respiratory cycle, but this capability has not been found necessary. As part of this work we have developed a package of cardiac imaging options, which includes:

1. 5-section, double spin echo imaging in approximately seven minutes.

2. 10-section single echo imaging in seven minutes.

3. Five or 10-section imaging showing each section at five points in the cardiac cycle in 35 minutes (cycled multi-section).

4. Fifteen-section at one point in the cardiac cycle in 68 min, with a capability of section thickness as small as 1.8mm. Regular thickness for all modes is 7mm. Currently spatial resolution in these sequences is 1.7mm, and is in the process of being doubled to 0.8mm.

Regular section thickness imaging of 127 patients and volunteers has shown the coronary arteries depicted as low intensity structures as follows: right coronary artery (RCA) seen on cross-section in 78.6 percent of subjects and origin of RCA seen in 50 percent of subjects; left coronary artery (LCA) - origin seen in 55 percent of subjects and bifurcation of LCA seen in 12.8 percent; left anterior descending coronary artery - seen either in cross-section or longitudinally in 48.6 percent of subjects; left circumflex artery seen in 23.6 percent of subjects.

Thin-section imaging of the heart in five volunteers shows comparable results. The thin sections present advantages (less partial volume averaging) offset by disadvantages: For vessels crossing from one section to another at a shallow angle visualization through the various sections is difficult, since each section contains a small portion of the vessel.

BEST COPY AVAILABLE

Further experimentation with intermediate thickness sections may be needed to optimize coronary artery imaging.

The second major component of this project involves the development of algorithms for reconstruction of vasculature in three dimensions, starting from a single set of tomographic images. Most of the work has been done in the abdomen. The algorithm identifies vessels by their characteristic NMR signature, and determines the patent area and depth in the body of each vessel. Connections and bifurcations are searched for, to establish contiguity of different vessels.

Vessels can be then displayed from any direction, with gray scale intensity or color coding depth. Vessel systems can be separated and displayed independently. The display can show the width of the vessel as it projects onto the viewing plane, or can show the diameter corresponding to a circular cross-section of the vessel, i.e., the image encodes true patent area. Also, patent area can be color coded on the vessel. Vessel systems or individual vessels can be separated by color. Using this algorithm we are currently in the progress of comparing the clinical efficacy of NMR and angiography in 15 patients. We have also started work to extend the process to the thorax and neck.

In conclusion: NMR imaging shows promise as a noninvasive modality for visualization of the coronary arteries and may eventually be useful for assessment of proximal occlusive coronary artery disease. NMR imaging is also certain to replace large vessel angiography in many applications.

Leon Kaufman, Ph.D.

Lawrence E. Crooks, Ph.D.

Charles Higgins, M.D.

James Hale, B.A.

BEST COPY AVAILABLE

MAYO FOUNDATION
Quantification of Coronary Artery Stenosis with the DSR
CONTRACT NUMBER: N01-HV-38042

The main feature of this contract is the replacement of the current Image Isocon based image chains with CCD based image chains. Preliminary evaluations of an Oldelft NA 0.48 objective lens and a microchannel plate based image intensifier coupled via tapered fiber optics to a CCD T.V. camera show that the new image chain characteristics meet the theoretical needs for intravenous coronary arteriography. The objective lens delivers five times more light photons to the first photo electric surface (intensifier) and the intensifier/tapered fiber optic bundle system delivers an adequate intensity of light to the CCD T.V. camera to permit full use of its intrascene dynamic range. The CCD camera sensor will be cooled with a thermo-electric cooling chip to around 0°C so as to ensure 1000:1 intrascene dynamic range in the video data.

In addition to the replacement of the image chains, we are developing and implementing specially adapted reconstruction algorithms which overcome some of the artifacts caused by limited number and range of angles of view. This will be particularly important if patients have irregular heart rates during a scan, thereby reducing the effectiveness of gated reconstructions.

The main attractions to a tomographic method for imaging coronary arteries following a right sided injection of contrast medium are that the problem of superposition is eliminated and that all angles of view are available from a single injection of contrast agent. This was demonstrated with a specially fabricated radiological phantom which is a very life-like chest. The ribs and spine are from a 75kg male, the heart and lungs are porcine and the chest wall and upper abdominal contents are made of 'dry' water. The left heart chambers, aorta, and coronary arteries contain approximately 1:10 diluted contrast agent so as to simulate the levophase from a right sided injection of contrast agent. A 3mm tract allows a catheter to be advanced via the superior vena cava, right atrium, right ventricle, and RVOT. The 2mm lumen of this catheter can be modified with 'stenoses' of different lengths and severity and the lumen filled with contrast agent diluted to any desired level. Scans of this phantom with the currently configured DSR demonstrate the power of the tomography based technique.

E. L. Ritman, M.D., Ph.D., Principal Investigator; Co-Investigators: R. C. Bahn, M.D., Ph.D., A. A. Bove, M.D., Ph.D., S. Dimolitsas, Ph.D., L. D. Harris, Ph.D., P. B. Heffernan, Ph.D., R. A. Robb, Ph.D., H. C. Smith, M.D.

BEST COPY AVAILABLE

STANFORD UNIVERSITY
(Hansen Laboratories of Physics and School of Medicine)

K-EDGE SUBTRACTION ANGIOGRAPHY WITH SYNCHROTRON X-RAYS

CONTRACT # N01-HV-38039 & GRANT # 1R01 HL 29824-01A1

The purpose of this program is to conduct an evaluation of tunable synchrotron X-ray beams for use in K-edge digital subtraction angiography of coronary arteries in humans. Activity in the first year has centered on an expansion of the X-ray beam line and of the imaging apparatus to accommodate human subjects.

Detailed engineering studies of the modifications required to a wiggler-illuminated X-ray beam at the Stanford Synchrotron Radiation Laboratory (SSRL) to increase the angular width from 0.75 to 4.6 mr began in December 1983. Delivery of the wide beam (12.5 cm in the initial operating location) at full intensity is expected in January 1985. A design concept for a fast-switching X-ray monochromator of matching width has been developed and completion of fabrication is expected by November 1984. A minimum line-exposure cycle time of 2 ms is specified for this device. The design of a room, 5 m x 3 m x 2.7 m, for angiography studies is complete and room assembly at SSRL is expected in September 1984. An operating procedure to provide for patient safety has been developed.

Expansion of the imaging apparatus includes the fabrication of a multichannel Si(Li) X-ray detector 15 cm in width (300 channels), the provision of the associated electronic amplifiers and digitizers, the upgrading of the data acquisition and display system to record and process human subject images in real time, and the design and fabrication of a patient-positioning and scanning apparatus, or chair. Completion of all these items is expected on a schedule that will permit the efficent test and evaluation of the new imaging apparatus immediately followng the commissioning of the new X-ray beam.

In vivo canine studies with the previous 2 cm wide beam were continued in the period March 13 to April 2, 1984, at a scan speed (line exposure cycle time of 8 ms) twice that used previously. The suppression of electronic image noise by a method of line-frequency synchronization proved to be very effective. These intravenous studies, mostly in the lateral projection, employed power injection, R wave triggering and, for some animals, the suspension of respiration. Also, for some animals, reference aortic root studies were performed.

Instrumentation studies were also conducted to demonstrate the dependence of image quality on the spacing between the energies of the two X-ray beams, and to define the level of veiling-glare due to X-ray scatter in the Si(Li) detector.

R. Hofstadter, Ph.D., Principal Investigator
E. B. Hughes, Ph.D., Associate Investigator
E. Rubenstein, M.D., Associate Investigator
H. D. Zeman, Ph.D., Associate Investigator
M. Buchbinder, M.D., Associate Investigator
D. C. Harrison, M.D., Associate Investigator
A. C. Thompson, Ph.D., Associate Investigator
G. S. Brown, Ph.D., Associate Investigator

BEST COPY AVAILABLE

UNIVERSITY OF PITTSBURGH
Development and Evaluation of Minimally Invasive Systems for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries in Humans
CONTRACT NUMBER: NO1 HV 38041-01

Research, development and clinical evaluation of an improved high-speed system of diode array digital radiography is proposed in order to achieve a minimally invasive detection and quantification of atherosclerotic lesions in human coronary arteries. This proposed method is based on an approach whose feasibility was demonstrated at the University of Pittsburgh under contract to the National Heart, Lung and Blood Institute. A more advanced system is now proposed which involves the use of two parallel x-ray beams produced by a dual focal spot tube illuminating two narrow phosphor screens fiber-optically coupled to self-scanning diode arrays. The output of the diode arrays are sent to a digital computer for processing and display of digital radiographic images of blood vessels containing small amounts of iodinated contrast media as produced in an intravenous injection. As in the earlier prototype, the x-rays are collimated to form thin, fan-shaped beams that allow highly efficient rejection of scattered x-rays, thereby maximizing the ability to detect the small amount of contrast media that is found in the intravenously filled coronary arteries. Our digital technique has already allowed us to produce high resolution images of the rapidly moving coronary arteries from an intra-aortic injection of contrast material, demonstrating the potential of the digital diode technique, which arrests the motion due to the millisecond line-by-line exposure. We have also succeeded in visualizing portions of the coronary arteries with an intravenous injection using our technique, but the effects of overlying pulmonary vessels and ventricles prevented us from seeing the entire length of the arteries. In the present proposed system, the use of two closely spaced x-ray beams and solid state detection systems will allow us to use precision motion subtraction of images. The advantage provided by the use of two closely spaced detectors is that two images can be produced in the same heart cycle that are recorded 150 milliseconds apart, allowing one to remove the fixed structures and vessels in the lung but not degrading the coronary arteries. This is because in the short time between the two images, the coronary arteries move but the pulmonary vessels remain stationary.

During the past year, research, development and construction of the dual beam diode array digital radiography system has been undertaken. This will enable the recording and display of subtracted digital intravenous coronary artery images with 1024 x 1024 pixels over our wide bandwidth television monitor. As part of this research the U-arm assembly of the x-ray table is being interfaced to a small computer enabling images to be taken with the patient stationary and the apparatus moving which should further improve the quality of the images.

Donald Sashin, Ph.D., Principal Investigator
Klaus M. Bron, M.D., Coprincipal Investigator

BEST COPY AVAILABLE

ARIZONA HEALTH SCIENCES CENTER, UNIVERSITY OF ARIZONA
Research, Development, and Evaluation of Minimally Invasive Systems for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries of Humans
CONTRACT NUMBER: NO1 HV 38046

This paper analyzes the factors involved in the noninvasive quantification of atherosclerosis. It is the objective of the University of Arizona imaging program to detect a 25 percent stenosis in a 2-mm diameter coronary artery. This paper identifies major problems associated with current imaging systems and procedures. They are: (1) spatial resolution; (2) low absorption of x-rays resulting in a low DQE; (3) low inherent contrast resulting from intravenous injection; (4) low contrast resulting from scatter effects. Improvements are necessary and possible in each of these areas: (1) The spatial resolution can be improved by selecting an image intensifier employing proximity-type focussing. (2) The x-ray absorption can be improved by selecting a scintillator with increased thickness. (3) The contrast factor can be improved with a proximity-type image intensifier by using fiberoptic windows at the intensifier's input and output. (4) Additional contrast improvement will result from an improved scatter grid or from application of airgap techniques. (5) The inherent x-ray contrast may be improved by selecting a different injection method. This paper describes the design considerations of a six-inch proximity focussed x-ray image intensifier with an external scintillator (CsI) and six CCDs coupled to the intensifier via fiberoptic tapers.

Theron W. Ovitt, M.D., Principal Investigator
Hans Roehrig, Ph.D., Senior Investigator

BEST COPY AVAILABLE

THE UNIVERSITY OF WISCONSIN
CLINICAL SCIENCE CENTER
Research, Development and Evaluation
of Systems for Noninvasive Detection
and Quantification of Atherosclerotic
Lesions in Peripheral and Coronary
Arteries in Humans
CONTRACT NUMBER: NO1 HV 12905

The overall objective of this contract is to develop a system for intravenous DSA of the coronary arteries. During the first year of this four year program, progress has been mainly in the area of apparatus development.

A new digital-video image processor has been completed and used for initial animal studies. This processor contains three 1024^2x12-bit memories and special purpose hardware which is designed to easily test new imaging algorithms which can be programmed to proceed in real-time. The system is interfaced to a digital disc capable of storing 30 512^2 images or 7.5 1024^2 images per second.

In addition to ECG-gated phase-matched mask mode and high-pass filtering, which have already begun to be investigated, dual-energy imaging will be implemented during the second year. Two modes, one with closely spaced ECG-gated exposures and another continuous mode which provides 15 energy subtraction images per second are planned. The latter mode has been added to our original plans based on our early impressions that continuous display is beneficial in distinguishing coronary arteries from complex background structures.

An adaptive temporal filtering algorithm has been implemented and is undergoing initial tests using computer-generated contrast-pass curves. The aim of this algorithm is to distinguish between pulmonary and coronary vessels based on the temporal history of each picture element. Several curve comparison and pixel suppression schemes will be simulated and tested using dogs.

Work on a compensating filter prepared using a computer-controlled dot-matrix printer with a cerium oxide ribbon has produced extremely encouraging results in connection with a Humanoid chest phantom. We are constructing a faster multi-head printer which will be permanently mounted in an experimental chest radiography installation. Filters will also be fabricated on this device using image-intensifier data and manually positioned on our fluoroscopic apparatus to test the effects of such filters in intravenous coronary angiography.

Charles A. Mistretta, Ph.D., Principal Investigator

BEST COPY AVAILABLE

STANFORD UNIVERSITY
Visualization & Quantitation of Coronary Arteries Using
Multiple-View Energy Subtraction Digital Radiography
CONTRACT NUMBER: NO1-HV-38045

Intravenous subtraction angiography, as currently practiced, is unable to visualize coronary arteries because of inadequate SNR, motion artifacts and obscuring intravening structures including pulmonary vessels and heart chambers. We are studying an approach which overcomes each of these problems to enable minimally invasive visualization of these vessels. A system of digital tomosynthesis is used where a conventional digital fluoroscopy system is rotated around the patient, enabling an array of images to be acquired at different angles. Each acquisition is timed with the ECG so that the resultant vessel images will be effectively stationary. The images are combined in the computer to isolate the plane of interest containing the desired coronary arteries. Other planes are blurred, thus removing the structures of the pulmonary vessels and heart chambers. The SNR is significantly improved by the square root of the number of angular views. The soft tissue structures are removed using dual-energy acquisitions at each view.

Phantom studies have been used to determine the required number of views. Controlled bolus systems have been considered for lengthening the bolus time to accommodate sufficient views. Scatter cancellation systems have been analyzed and tested for more accurate soft tissue subtraction. Improved noise-reduction algorithms have been implementing for removing the noise penalty associated with dual-energy systems. Efficient algorithms have been studied and implemented for outlining blood vessels in poor SNR environments.

Albert Macovski, Ph.D., Principal Investigator (W.R. Brody, co-P.I. on leave)

BEST COPY AVAILABLE

MAYO FOUNDATION
The DSR, Status Report '84
GRANT NUMBER: PO1 HL04664-23A1/24

Project I - Show that in children with congenital pulmonary atresia location and area of distribution of pulmonary perfusion by various developmental and surgical systemic to pulmonary arterial shunts can be demonstrated with a single injection of contrast medium into the root of the aorta.

Project II - Potential mismatch between lung geometry and chest wall geometry of dogs with intact chest before and after pneumothorax while maintaining the same intrathoracic air content. Results to date clearly show little change of chest wall (including diaphragm) geometry when prone but marked change in the supine animal.

Project III - Eight human volunteers were scanned awake, anesthetized, and anesthetized paralyzed. The data suggest that reduced lung capacity during anesthesia is due primarily to movement of the diaphragm into the thoracic cavity.

Project IV - Major improvements in display of organ surfaces (e.g., endocardium or epicardium) have been developed and the algorithms optimized for rapid execution. The addition of color coding to the displays increases the information content of the display.

Project V - The varifocal mirror display system is operational. It is used to display an entire volume image, operator interactive windowing, and related manipulation of the image.

Core A - The DSR scanner has been improved in several ways -
(a) Digital encoding of scan related information into the video scan lines. This information allows for reproducible transfer of video image sequence from video tape to video disc.
(b) This encoded record also stores the x-ray current and pulse width so that scene-to-scene dynamic range of the recorded video image by varying x-ray intensity 4-5 fold so as to maintain constant image intensity over the region of interest.
(c) Implementation of cardiac scan mode where the vertical extent of the video raster is reduced to only 11cm of axial height resulting in scanned slice thickness 0.9mm in the high and 0.45mm in lower temporal resolution scan mode.

Core B - The ModComp computer system continues to be upgraded. The implementation of the header record (see Core A) greatly facilitates ECG or pressure waveform gated reconstruction.

Core C - The image analysis programs developed on the Cyber computer are now being implemented on Charles River System based microprocessors. These workstations should greatly increase data analysis throughput.

Core D - Administrative Support -

Erik L. Ritman, M.D., Ph.D., Project Director; Douglas D. Mair, M.D., Joseph R. Rodarte, M.D., Kai Rehder, M.D., Richard A. Robb, Ph.D., Lowell D. Harris, Ph.D., Project Principal Investigators

BEST COPY AVAILABLE

BAYLOR COLLEGE OF MEDICINE
Ultrasonic Instrumentation for Cardiovascular Studies
GRANT NUMBER: 5 RO1 HL 22512-07

To eliminate the need for intramyocardial transducers in measuring regional left ventricular (LV) function and to estimate the transmural distribution of LV thickening, we are developing an ultrasonic pulsed Doppler instrument which utilizes a single 10 MHz epicardial transducer. Wall thickening is evaluated by digitally integrating the velocity of myocardial layers passing back and forth through each of eight sequentially range-gated sample volumes distributed across the LV wall. The resulting displacement waveforms represent the amount of thickening between the epicardial transducer and each range gate. With the Doppler audio bandwidth extending from 1 Hz to 1 KHz, velocities from 0.08 to 80 mm/s can be processed; and using a four-quadrant zero crossing counter, resolution is 1/8 wavelength or 0.02 mm.

To determine whether there are systematic differences in endo/epi thickening over the surface of the left ventricle, we used a vaccuum attached probe mounted in a small suction cup to map the transmural distribution of LV thickening in acute dogs. With the ventricle divided into basal, central, and apical regions, our initial results in three dogs show significant differences in thickening vs depth curves. Although the total wall thickening fractions in each region are similar, thickening is uniformly distributed across the wall in the central region, but is greater in the inner layers in both apical and basal regions. Thick walled models predict that there should be more thickening in the inner layers, and on the average out data agree. However we do not yet have a model which predicts uniform thickening even in particular regions.

We also used the Doppler technique to study the response and recovery of inner and outer wall function in seven conscious dogs following 15 minutes of coronary occlusion and 3 days of reperfusion. We found that in general the inner wall thickens more than the outer wall, and undergoes greater disfunction with ischemia. During reperfusion the outer wall recovers within 1 hour, but the inner wall function is still significantly depressed after 1 day returning to control values only after 3 days.

In addition to the animal studies, we are beginning a study in patients to evaluate regional myocardial function intraoperatively using the vaccuum attached probe tested in the acute dog study. Our initial goal is to measure thickening in several regions before and after aorto-coronary artery bypass procedures. The non-revascularized areas will serve as controls for the effects of cardiopulmonary bypass on cardiac function. There are currently no quantitative methods for evaluating regional myocardial function in patients in an atraumatic manner.

Craig J. Hartley, Ph.D., Principle Investigator
Robert M. Lewis, Collaborating Investigator
Mark L. Entman, M.D., Collaborating Investigator
George P. Noon, M.D., Collaborating Investigator
Robert M. Nerem, Ph.D., Collaborating Investigator
Lloyd, H. Michael, Ph.D., Collaborating Investigator

BEST COPY AVAILABLE

GEORGIA INSTITUTE OF TECHNOLOGY,
Hemodynamics of Normal and Diseas Carotid Arteries.
Grant Number: ROl HL 22835-05.

The research program is designed to study flow in the normal and diseased human carotid bifurcation and to develop signal analysis techniques which allow extraction of flow field information useful in noninvasive diagnostic measurements with Doppler ultrasound. Steady and pulsatile flows in a model of the human bifurcation have been investigated using laser Doppler anemometry. These studies have delineated important differences between steady and unsteady flow behavior. Although flow separation occurred under steady conditions with a resulting region of continual low wall shear, pulsatile flow produced oscillatory wall shear during systole so that no permanent separation region existed. Flow "disturbance" included strong helical patterns and organized three dimensional configurations, particularly during the latter part of systole. However, the bifurcation model showed no turbulence over the physiological range of flow conditions studied. This phase of the work will continue with the investigation of flows in models of bifurcations which incorporate lesions. Comparisons of the model data with noninvasive velocity measurements using pulsed Doppler ultrasound in human subjects show that the features seen in the module also occur in humans.

Flow disturbance analysis methods have focussed upon (i) improving the determination of underlying velocity waveforms by phase shift averaging; (ii) examining high velocity disturbance through autoregressive modelling; and (iii) separation of low and high frequency components through homomorphic filtering. We have found that the underlying velocity structure may be modelled with a fairly small number of parameters using autoregressive models. Of particular importance at low degrees of stenosis are coherent starting structures (not to be confused with coherent structures in transitional or turbulent phenomena). Also, through the hormomophic filtering method we have been able to separate vortex shedding phenomena from higher frequency velocity oscillations induced by vessel wall vibration.

The results to date indicate that it may be possible to characterize relatively mild degrees of stenosis using the low frequency content of flow disturbance. Future work is to be directed toward the problems associated with geometric and flow variability which can mask pathological disturbance.

Don P. Giddens, Ph.D., Principal Investigator.
Richard I. Kitney, Ph.D., Collaborating Investigator.

BEST COPY AVAILABLE

BOWMAN GRAY SCHOOL OF MEDICINE
UNIVERSITY OF SOUTH CAROLINA
LOUISIANA STATE UNIVERSITY
Noninvasive Assessment of Pediatric Atherosclerosis
GRANT NUMBER: 1 RO1 HL 26554-04

Previous pathological studies of atherosclerosis in an animal model (M. fasciculatis) have demonstrated that a high cholesterol diet will produce significant preclinical cornary artery disease after a relatively short period of]8 months on the diet. An elevated systolic blood pressure was also present in these animals relative to controls. Noninvasive detection of the coronary disease was not achieved prior to necropsy.

Very early carotid artery disease was also found to be present in these animals at necropsy. While not resulting in a narrowed lumen, the disease was found to produce a significant stiffening of these arteries compared to controls. This stiffness was measured prior to necropsy using non-invasive ultrasonic techniques and standard blood pressure measurements.

Recently, similar measurements were made on the carotid arteries of a subpopulation of the Bogalusa Heart Study. Children were selected for study based upon their values of the two risk factors (cholesterol and blood pressure) arising in the studies described above on M. fasciculatis. A high risk group was selected which had values of both total serum cholesterol and systolic blood pressure in the top tertile for their sex-race group as determined in two previous screenings. The low risk group was selected to have these parameters in the bottom tertile. The ages ranged from 10 to 16 years. Preliminary data illustrating the differences in carotid artery stiffness observed in the white population studied are given below.

Sex	Male		Female	
Risk	High	Low	High	Low
Mean Age, yrs.	13.3	12.9	12.8	13.3
Mean Systolic Pressure, mmHg	114	95	115	94
Total Serum Cholesterol, mg/dl	199	124	192	130
Arterial Stiffness, kPa (mean ± sem)	67 ± 3	61 ± 2	61 ± 3	50 ± 2

These results suggest that physiologically significant changes may already be occuring in the carotid arteries of children possessing elevated levels of adult risk factors by the beginning of the teenage years. Taken together with the earlier studies on M. fasciculatis, the results suggest the potential use of this technique in identifying individuals highly susceptible to atherosclerosis at an early period of life where therapeutic intervention could be most effective.

Ward A. Riley, Jr., PhD., Principal Investigator
David Freedman, Ph.D., Collaborating Investigator
Gerald Berenson, M.D., Collaborating Investigator
Ralph W. Barnes, Ph.D., Collaborating Investigator

BEST COPY AVAILABLE

UNIVERSITY OF IOWA
Assessment of In Vivo Passive Myocardial Stiffness
GRANT NUMBER: 2 R01 HL 27035-03

The passive elastic behavior of the myocardium is one of the factors which determine left ventricular (LV) diastolic properties and which have important implications for ventricular function in a variety of clinical circumstances. In this project, we are using a combined ultrasonic/hemodynamic technique for the reconstruction of the three-dimensional geometry of the LV and the estimation of the myocardial elastic properties using the finite element technique. Our major goal for this grant year is to assess the changes in passive myocardial elastic properties in regions of acute ischemia induced by the occlusion of the circumflex coronary artery in an open chest canine model. Cross-sectional echocardiographic images of the canine LV are recorded with the echo transducer mounted in a specially designed articulated arm so that the relative orientation of the images are known from the readings of the six potentiometers mounted on the arm. LV pressure is measured using a high fidelity catheter-tipped transducer. Three-dimensional LV geometry is reconstructed with the aid of a computer from 8-12 short axis images. Using the data from early and late diastole, we estimate the myocardial elastic modulus using the finite element technique and an optimization algorithm. Repeating the experiment after the occlusion of the circumflex artery, our analysis technique is able to identify regions of increased elastic modulus which correlate with the distributional (risk) area of the occluded artery.

During this grant year, we also propose to apply this method to images acquired from a fast CT scanner in the animal model. This technique enables us to acquire 8-12 parallel images of the LV within a few consecutive cycles where the endocardial and epicardial edges are more clearly defined than those obtained with the present generation ultrasonic scanners.

Krishnan B. Chandran, D.Sc., Principal Investigator
David J. Skorton, M.D., Co-Principal Investigator
Steve Collins, Ph.D., Co-investigator
Richard Kerber, M.D., Consultant
Melvin Marcus, M.D., Consultant

BEST COPY AVAILABLE

MEDICAL COLLEGE OF WISCONSIN
Noninvasive Cerebral Blood Flow Measurement
GRANT NUMBER: R01 HL/NS 27130-03

Noninvasive volumetric blood flow measurement using nuclear magnetic resonance (NMR) techniques is accomplished with continuous - wave radiofrequency excitation. For the measurement of cerebral blood flow, a 63.5 cm I.D., 1.1 meter long warm-air for superconducting magnet (variable from 0 to 20,000 gauss) is employed. For current studies, a magnetic field of 5026 gauss (21.4 MHc) is used. Liquid helium is maintained in the magnet by a recycling helium liquefier. Liquid nitrogen jacket cooling is not required, and cool-down of the magnet can be accomplished simply with liquefication of gaseous helium by the helium liquefier.

Two types of crossed-coil NMR detectors have been used. The first type of detector has a flat geometry, and can be placed on the surface of the body to measure flow in vessels directly below it. A ranging technique was implemented, using oscillating gradient magnetic fields, to focus on specific arteries. This method enabled flow to be measured in the carotid arteries (common, internal, and external) as well as in the middle of cerebral artery (using signal averaging techniques). A two-dimensional scanning technique, also using oscillating gradient magnetic field, has been used to produce an image of blood flow in the carotid artery.

The second type of NMR detector has a cylindrical geometry. The transmitter and receiver coils are mounted on a plastic tube, into which the head can be inserted. This type of detector has the advantage of a nearly uniform sensitivity throughout the volume of the head. In contrast, the flat crossed-coil detector has a decreasing sensitivity both perpendicular to and parallel to the surface of the skin. The cylindrical crossed-coil detector is currently being evaluated in vitro.

Joseph H. Battocletti, Ph.D., Principal Investigator
Anthony Sances, Jr., Ph.D., Co-Investigator

BEST COPY AVAILABLE

UNIVERSITY OF PITTSBURGH
Local Cerebral Blood Flow by Serial CT Imaging
GRANT NUMBER: 1 R01 HL 27208-03

We are studying the measurement of local cerebral blood flow (LCBF) by the use of computerized tomography during and after the inhalation of nonradioactive (stable) xenon gas in the baboon. The method has provided LBF information with a relatively high degree of spatial resolution and anatomical correlation.

With the computer, we calculate a blood flow value for each CT volume unit (voxel). By reference to a gray or color scale, the computer then produces blood flow maps with high resolution (FWHM ≤ 5 mm) which correlate to anatomical structures. The flow information derived from these maps corresponds to the physiological condition of the subject and has equally good resolution and sensitivity for superficial and deep brain regions. We simultaneously compute the partition coefficient for each unit of tissue volume in an effort to increase accuracy and the applicability of this method to diseased and abnormal tissues. The rapid multi-level CT scanning used in these studies permits examination of blood flow within multiple brain levels during a single 4-6 minute xenon inhalation. We have developed the ability to reconstruct from these multiple levels a display of LCBF in three dimensions in any preselected region of interest with a spatial resolution of 5mm or better in each direction (x, y, z).

This method has been used to measure changes in LCBF that occur after pharmacologic and surgical manipulation. Blood flow maps are also able to demonstrate progressive increases in local blood flow which result from progressive elevations of $PaCO_2$ as well as regional reductions in flow which result from surgical ablation of perforating branches of the middle cerebral artery.

We have investigated the validity of the xenon technique and the effect of xenon inhalation on blood flow in studies comparing the xenon gas method and the microspheres method in the measure of LCBF, using the same tissue volumes and under similar conditions. The results of the combined data indicate that an overall association between the two methods exists ($P<0.0005$).

Future efforts ir this project will concentrate on establishing the validity and accuracy of this method in low blood flow states.

David Gur, Principal Investigator
Sidney K. Wolfson, Jr., Co-Principal Investigator
Howard Yonas, Investigator
David L. Jackson, Investigator
Walter F. Good, Investigator
Richard E. Latchaw, Investigator
William H. Kennedy, Investigator
Eugene E. Cook, Investigator
Barbara C. Good, Investigator

BEST COPY AVAILABLE

PENNSYLVANIA STATE UNIVERSITY
Dynamic Radiographic Assessment of Myocardial Function
GRANT NUMBER: 2 RO1 HL 27437-03

Regional wall dynamics, wall thickening, and myocardial perfusion patterns provide sensitive measures of ventricular performance and its correlation with myocardial infarction and ischemia. Nevertheless, techniques currently available for obtaining such measurements are often expensive, invasive, or of limited resolution. A new technology (dynamic radiography), based upon the analysis of secondary radiation fields (scattered and fluorescence), for obtaining such data is under development.

Three-dimensional epicardial wall dynamics are measured using a seven-detector array to interrogate x-rays scattered from the epicardial surface. Real time dynamic displays of epicardial surface contours are shown on a CRT screen. Scan times (close-chest canines) from initiation to data display are under 10 seconds. Epicardial surface location is accurate to 0.2 mm (S.D.) and local wall displacements to 0.1 mm (S.D.). Surfaces behind or in front of the cardiac silhouette are located with equal accuracy.

Wall thickness measurements are accomplished with a two-detector array. Radiation scatter is used to measure epicardial dynamics and x-ray induced fluorescence from the blood pool - myocardium interface is used to measure the dynamics of the endocardium. A prototype has been tested on mechanical models and experimental animals (dogs). Measurements of epicardial and endocardial wall excursions and percent wall thickening agree with the results of others.

Myocardial perfusion measurements are also obtained with a two-detector system. A sodium iodide detector monitoring x-ray scatter from the epicardial surface is used to guide a germanium spectrometer such that its collimated field of view is restricted to tissue locations on the myocardial free wall. Iodine fluorescence measurements are made subsequent to an intravenous injection of contrast agent. Measurements of local static and dynamic contrast distributions have been carried out on mechanical models, excised canine and pig hearts, and in open- and close-chest canine preparations (with and without coronary ligations) to show regional perfusion patterns.

The development of this dynamic radiographic technology should result in a combined diagnostic system capable of measuring submillimeter ventricular wall dynamics, myocardial perfusion patterns, and ventricular wall thickening. Radiation dose levels (<250 mr) are low and component costs (<20K) for the current prototype systems were modest.

Joseph J. McInerney, Ph.D., Principal Investigator
Edward S. Kenney, Ph.D., Co-Investigator
Robert F. Zelis, M.D., Co-Investigator

BEST COPY AVAILABLE

UNIVERSITY OF PENNSYLVANIA
Development and Testing of Clinical Blood Viscometer
GRANT NUMBER: 5 R01 HL 28105-02

We have completed development and are currently testing clinically a viscometer capable of measuring the shear dependent viscosity of whole fresh blood. The device employs an unsteady capillary flow and is capable of measuring blood viscosities over shear rate range of 1 to 1000 inverse seconds. On any individual run a shear rate range on the order of 50 to 1 can be covered. Because each experiment takes on the order of 15 to 60 seconds no anticoagulants are needed. The device incorporates a digital recording and analysis system which can provide immediate analysis of the results and fitting of the data to different blood rheological models. Currently, Power Law and Casson model parameters are available as well as calculations of apparent viscosity at any desired shear rate. Individual samples are reproducible to better than one percent with predicted parameters on repeat samples being reproducible to about one percent. The instrument is currently being evaluated at a number of clinical locations and with subjects from various types of studies, including: (a) studies of blood viscosity parameters in stroke and in hemodilution methods for treating stroke; (b) evaluation of whole blood rheology parameters in sickle cell anemia; and (c) evaluation of whole blood rheology in peripheral vascular disease.

Mitchell Litt, D.Eng.Sc., Principal Investigator
John Seybert, Research Fellow

BEST COPY AVAILABLE

UNIVERSITY OF PENNSYLVANIA
Computer Technology for Transaxial Tomography
5 R01 HL 28438-04

This is a continuing project on computer technology for transaxial tomography devices. Attention is being given to reducing the required time, cost, and dose for improved reconstructions, especially from data obtained either from rapidly moving objects (heart) or from large amounts of data covering the whole extent of a big organ (lungs), and to the displaying of the results obtained from such data in a truly effective way. This is done by (i) improvements to an existing programming system and data base, (ii) use of optimization techniques, (iii) minicomputer implementation of an operator-interactive graphics systems, and (iv) development of special purpose algorithms for reconstruction from incomplete and/or limited view projection data. Continued cooperation with clinical facilities and manufacturers of computerized transaxial tomography equipment provides immediate medical application of our work. In particular, attention is paid to the needs of such state-of-the art developments as (i) low dose detection of cancer lesions, (ii) interactive surgical planning and (iii) reconstruction and analysis of the beating heart from echocardiograms.

In particular, during the last fiscal year of the grant we have published papers on reconstruction problems including (i) multilevel image reconstruction, (ii) entropy maximization, (iii) strongly underrelaxed ART for inconsistent systems, (iv) sparsely sampled data, (v) cone beam inversion, (vi) beam-hardening correction, and (vii) missing data, and on display problems including (i) interactive segmentation, (ii) representation of 3D data on 2D display, (iii) directed contour representation, (iv) computer architecture, (v) surface tracking, and (vi) application to craniofacial surgical planning.

Gabor T. Herman, Ph.D., Principal Investigator
Robert M. Lewitt, Ph.D., Co-Investigator
Nathaniel Reichek, M.D., Co-Investigator
Sushma S. Trivedi, Ph.D., Co-Investigator

BEST COPY AVAILABLE

THE PENNSYLVANIA STATE UNIVERSITY
Ultrasonic Scattering by Biological Tissues
GRANT NUMBER: 3 R01 HL 28452-02

This project is directed at furthering the understanding of scattering mechanisms of ultrasound in biological tissues. This understanding is crucial to the accurate interpretation of echographic appearance of tissue structures in images obtained by ultrasonic scanners.

Using a computerized experimental system which facilitates rapid data collection, attenuation coefficient and backscattering properties including backscatter at a single frequency (mainly at 7.5 MHz), backscatter over the frequency of 3 to 8 MHz, and intergrated backscatter over the same frequency range have been determined for various bovine tissues such as heart, liver, spleen, pancreas and normal human blood as a function of time during coagulation. In addition, these properties have also been measured for several types of pathological bovine tissues, namely, liver abscess and cardiac tumors. Following acoustical measurements, the tissues are examined histologically.

Preliminary results indicate that of the tissues studied, backscatter from liver is the highest while spleen has the lowest backscatter. Each tissue also exhibits a distinct frequency dependence. Backscatter from solid portion of liver abscess was found to be significantly smaller than that of normal liver whereas cardiac sarcoma and lymphoma typically have a backscatter less than that of normal myocardium.

Results on thrombus demonstrate that backscatter from thrombus of 12 hours old is at least 18 dB higher than that of blood over this frequency range. A comparison to the backscatter of bovine myocardium shows that myocardium is more echogenic than fresh thrombus and is less echogenic than thrombus of more than 12 hours old. Similar results were also obtain for integrated backscatter measurements.

Further investigations into the statistical nature of echoes backscattered from these tissues reveal that amplitude distribution of echoes from liver is governed by Rayleigh statistics. On the other hand, echoes from heart and kidney are Rician-distributed indicating the presence of a coherent component in the signal.

K. Kirk Shung, Ph.D., Principal Investigator
Terry M. Wilson, D.V.M., Collaborating Investigator
John Tarbell, Ph.D., Collaborating Investigator

BEST COPY AVAILABLE

UNIVERSITY OF MICHIGAN
Automatic Processing of Digital Echocardiography
GRANT NUMBER: 1 ROI HL 29716-01A1

We are presently developing and implementing new methods of direct line-mode digitization of two-dimensional echocardiography (2D echo) images. The envelope-detected RF signal is acquired in a digital format for further processing. We have investigated various image processing algorithms to perform time-varying edge detection. Presently, we are concentrating on an algorithm based on using Gaussian filtering to smooth the image both spatially and temporally followed by a Laplacian-like operation. These new algorithms use much larger windows than the 3 x 3 windows that are typically used.

To test our directly digitized images and edge detection algorithms, we have constructed a 2D echo cardiac phantom and a computer simulation of 2D echo images of the left ventricle in the short-axis projection. The cardiac phantom consists of synthetic tissue equivalent material containing 16 eccentric annuli of different echogenicity. The inner diameters of the annuli vary from 3.0 to 4.8 cm, outer diameters from 6.0 to 7.1 cm. Using standard video-based 2D echo, the diameters and areas of the 2D echo measures correlated highly with actual measurements ($r = 0.99$, $r = 0.98$, respectively). There was a downward bias of these measurements which appeared to be related to true physical beam spread and an underestimating boundary tracing rule.

We have also created a 2D echo model of the beating heart which has five parameters: cardiac chamber size, epicardium eccentricity, individual contraction rates for the endocardium and epicardium, and speckle. The backscattering effect of 2D echo, often referred to as speckle noise, was created using a Monte Carlo technique to populate a 2D random scatterer field. The scatterers were imaged by a 50% fractional bandwidth transducer with a position invariant, point spread function. Analysis of the detected envolope signal demonstrated Rayleigh statistics. A standard figure of merit was used as a performance measure for all automatic boundary techniques. Time varying edge operators had a 25 percent greater performance measure compared to classical operators.

Andrew J. Buda, M.D., Principal Investigator
Edward J. Delp, Ph.D., Co-Investigator
Charles R. Meyer, Ph.D., Co-Investigator
Fred L. Bookstein, Ph.D., Co-Investigator

BEST COPY AVAILABLE

UNIVERSITY OF UTAH
Tomographic Digital Subtraction Angiography
GRANT NUMBER: 1 RO1-HL31984-1

While subtraction image processing removes the majority of nonopacified vasculature in angiography, annoying patient motion and vessel overlap remain the predominant sources of image degradation. Classic (focal plane) tomography is being combined with digital subtraction angiography in an effort to overcome these present deficiencies. Initial animal studies using limited angle circular tomographic image acquisition have demonstrated that both patient motion and vessel overlap are largely mitigated with the incorporation of tomographic acquisition and tomosynthetic focal plane reconstructions.

The resulting tomosynthetic subtraction images are far from optimum, however. Blurred vascular image contrast from overlying planes still can compromise the image quality. For non-cardiac imaging an Iterative Least Squares Technique (ILST), "Ectomographic" image processing and Selective Plane Removal (SPR) are being studied in order to improve the present image quality. Relative performance of the three methods is being studied using circular tomographic geometry and eight and 16 projections. In a related study SPR image processing is being used in an effort to quantitate ventricular volumes from limited angle projection data.

A unique x-ray tube is being designed in order to perform circular tomographic imaging of the beating heart. The x-ray tube design incorporates a cylindrical stationary anode and stationary cathode with electronic beam steerage in order to produce a "moving focal spot" x-ray source that will permit the formation of focal plane tomographic images in .005 to .030 seconds. At the output of the image detector, an image intensifier, the light optics will be modified to "track" the projected motion of anatomy within preselected planes, thereby producing tomosynthetic images directly. A mechanical (galvanometer mirror scanner) and an electro-optical (optical image intensifier) are being studied as candidates for this tracking optical system.

Robert A. Kruger, Ph.D., Principal Investigator
James A. Sorenson, Ph.D., Collaborating Investigator
James A. Nelson, M.D., Collaborating Investigator

BEST COPY AVAILABLE

Therapeutic Instrumentation and Devices

BEST COPY AVAILABLE

BLANK PAGE

PENNSYLVANIA STATE UNIVERSITY
Elimination of Reoperative Cardiac Pacemaker Surgery
GRANT NUMBERS: 5R01 HL13988-12
5K04 HL00586-04

Extruded urethane tubing has largely replaced silicone as the insulation of choice on cardiac pacemaker leads. Although this urethane has been shown to be biocompatible, there have been reports of insulation defects. Our studies were on a Biomer-like segmented polyether polyurethane (SPU) which is solvent-dissolved (DMAC) and applied directly to the wire by a coextrusion process. By using this technique, small diameter, yet very strong, pacemaker leads can be made. The leads can be coated evenly and uniformly along their entire length. Because this SPU has a heat settable, memory-retaining characteristic, it is not necessary to build up extra material or have extra wire at the J-bend of atrial leads in order for the lead to maintain its shape and placement. The result has been the development of atrial leads of the same O.D. as standard ventricular leads (1.4 mm) and special purpose ventricular leads smaller than 1.0 mm and coaxial leads less than 2.3 mm. The stiffness and handling characteristic of each lead can be modified by varying the thickness of the polymer coating over essentially an infinite range. Furthermore, because there is a physical bonding of the SPU to the wire, the strength and elasticity of the polymer is added to that of the wire coils enabling them to flex together smoother and longer than extruded urethane covered leads. Stress-strain analysis consistently demonstrated a 7-25 times greater flex life when the SPU bonded leads were compared against identical wires covered with extruded tubing. There was no frictional wearing of this SPU polymer from the inside because the polymer and wire are bonded together and never rubbing against each other.

The results of the animal tests in rats, rabbits and dogs up to over three years demonstrated the long-term biocompatibility and nonthrombogenicity of this SPU. There was never any case of an adverse response in any animal. The leads remained thrombus and fibrosis-free along their entire transvenous length. Muscle and subcutaneous tissue responses were minimal. The response of the blood and vascular tissue to SPU was far less than that reported for silicone pacemaker leads. Polarizing light microscopy failed to show any indication of stress-induced light defraction. The leads have not shown stress-related features or any sign of developing crazing or cracking, either before or after any of the in vivo or in vitro testing. The pacing-sensing functions of the SPU leads remained at levels comparable to other lead systems.

The SPU has a high modulus of elongation (>700%), low creep, great strength (>6000 psi), memory retaining characteristics and great flexibility (>100 million cycles) making this SPU an ideal insulating material for pacemaker leads as well as many other biomedical applications. Coextruding the lead with the conductive wire results in a highly compliant, stress-free conductive system for pacemakers.

Howard C. Hughes, V.M.D., M.S., Principal Investigator.

BEST COPY AVAILABLE

UNIVERSITY OF MISSOURI
Waveform Dependency in Defibrillation
GRANT NUMBER 5 R01 HL 18040-09

Prior studies have shown that a broad category of symmetrical and asymmetrical bidirectional rectangular wave shocks are superior to the most favorable unidirectional rectangular wave shock in the transthoracic defibrillation of 100 kg calves. While convenient for research purposes because the various parameters can be specified easily, rectangular wave shocks are difficult to generate in clinical sized defibrillators.

Based upon our experience with bidirectional rectangular waveforms, we are currently studying symmetrical and asymmetrical bidirectional truncated exponential wave shocks which can be implemented in clinical sized apparatus.

In the first portion of the study, the effectiveness of waveforms in which the leading and lagging half-cycles were of equal duration was studied in 960 fibrillation-defibrillation episodes in 90-110 kg calves. The initial and final current amplitudes of the leading and lagging half-cycles and the total durations of the eight waveforms evaluated were respectively 70, 35, 35, 18 A-7.54 ms; 70, 35, 70, 35 A-7.54 ms; 70, 50, 35, 25 A-5.60 ms; 70, 50, 70, 50 A-5.60 ms; 70, 35, 18, 9 A-15.1 ms; 70, 35, 35, 18 A-15.1 ms; 70, 50, 18, 13 A-11.2 ms; and 70, 50, 35, 25 A-11.2 ms. These waveforms, involving delivered energy levels in the 250-500 joule range, yielded first-shock percent success levels of 87 through 100 percent in calves which had been fibrillating for 30 seconds. Four of the waveforms were 96-100 percent successful with the 70, 50, 35, 25 A-11.2 ms waveform being 100 percent successful. The second and third portions of this study, which are currently underway (August 1984), involve initial currents of 50 and 100 amperes.

Our data support the proposition that the bidirectional truncated exponential shocks are well behaved and that their performance in predictable from that of associated bidirectional rectangular wave shocks. Although there are uncertainties in extrapolating experience from the 100 kg calf to the human, we interpret the results of this and earlier studies as warranting clinical trials of bidirectional truncated exponential wave defibrillators.

John C. Schuder, Ph.D., Principal Investigator
Harry Stoeckle, M.D., Collaborating Investigator
Wayne C. McDaniel, M.S.E.E., Collaborating Investigator

BEST COPY AVAILABLE

NEWARK BETH ISRAEL MEDICAL CENTER
Thermal Control of Heart Rate
GRANT NUMBER: 5 R01 HL 23527-06

Arrhythmias, particularly sinus tachycardia, are often seen after open-heart surgery or in the course of an acute myocardial infarct. Pharmacologic agents are often ineffective to control these arrhythmias or may be contraindicated. Carotid sinus pressure and various types of pacing, such as rapid atrial pacing, paired or coupled pacing, and timed extrasystoles, are often ineffective, especially in febrile states.

In the operating room during open-heart surgery, we have seen that heart rate is easily and quickly controlled by slight local temperature changes of the sinoatrial (SA) node. We have evaluated this effect initially in an animal model using an open-chest preparation. Small cooling thermodes were designed to operate in conjunction with miniature thermocouples to cool and monitor the SA node. Initial data demonstrates the feasibility for varying SA node temperature in order to control heart rate within a clinically useful range.

A system has been developed which utilizes a micro-computer servo-system to control the flow of refrigerated saline to the thermode. Flow rate is controlled to maintain a pre-selected heart rate. The system used heart rate data obtained from limb leads and is electrically isolated. Evaluation in the dog has shown it to be simple to apply and use. Clinical trials are in progress.

Victor Parsonnet, M.D., Principal Investigator
David Glass, M.D., Collaborating Investigator
Alexander Villanueva, B.Sc., Collaborating Investigator

BEST COPY AVAILABLE

CASE WESTERN RESERVE UNIVERSITY
Defibrillator Waveshape Optimization
GRANT NUMBER: 5 R01 HL24606-05

The efficacy of cardiac defibrillation can be improved by increasing the safety factor (ratio between dysfunction inducing shock intensity and defibrillation inducing shock intensity) of the defibrillator waveform. This can be achieved either by increasing the current producing a specific degree of postshock dysfunction or by decreasing the current producing defibrillation. Previous studies showed that biphasic waveforms having low amplitude negative portions significantly reduce postshock dysfunction, increasing safety factor.

Our studies during the past year focused on the second method of improving safety factor---lowering defibrillation threshold. The currently accepted hypothesis is that defibrillation is achieved by exciting a critical mass of tissue, rendering the tissue non-excitable, and interrupting the circus movement. Consistent with this hypothesis, excitation thresholds for monophasic waveforms during diastole were used successfully to compare relative defibrillation thresholds (Jones et al, 1982). However, biphasic waveforms, which do not significantly alter the diastolic excitation threshold when compared with the corresponding monophasic waveform, significantly reduce defibrillation threshold (up to 60% of the value for the corresponding monophasic waveform; Schuder, 1983). In reconciling this apparent conflict between the defibrillation hypothesis and experimental results, we hypothesized that a conditioning hyperpolarizing prepulse might increase the efficacy of stimulation during the refractory period. To test this hypothesis, we compared the effect of monophasic and biphasic waveform stimulation during diastole and during several stages of the refractory period in cultured myocardial cells and in Purkinje fibers. During diastole, excitation thresholds were similar for monophasic and biphasic waveforms. However, during latter phases of the refractory period, the biphasic waveform significantly prolonged total refractory period when compared to the control monophasic waveform. At a stimulus interval of 275 msec, a biphasic stimulus 4 times diastolic threshold produced a total action potential duration which was 1.5 times the duration produced by the positive portion only. In contrast, at 175 msec, no action potential prolongation was produced by either monophasic or biphasic waveforms. These experimental results agreed with those obtained theoretically using a modified Beeler and Reuter model of the ventricular action potential.

The increased efficacy of biphasic waveforms in exciting partially refractory cells can explain in part the decreased defibrillation threshold produced by these waveforms, since the effect is greatest in those cells which could not be excited by a monophasic waveform, but would then become excitable to continue the circus movement.

Janice L. Jones, Ph.D., Principal Investigator
Ronald E. Jones, M.S.E.E., Co-investigator

BEST COPY AVAILABLE

CASE WESTERN RESERVE UNIVERSITY
Defibrillator Induced Dysfunction
GRANT NUMBER: 5 R01 HL26924-04

Previous experiments demonstrated that post-countershock refibrillation, evidenced by a failure to defibrillate, is produced by a shock-induced, prolonged depolarization of the myocardial cell membrane lasting up to several minutes. Preliminary experiments with cultured myocardial cells suggested that this depolarization was associated with transient sarcolemmal microlesions, since 10K molecular weight FITC-dextrans were found intracellularly following 6-200 V/cm, 5 msec, rectangular wave electric field stimuli, but not following 100 V/cm stimuli. Therefore, the goal of the present experiments was to confirm this finding, to determine whether 4K dextrans were incorporated at 100 V/cm, and to define the localization of these microlesions on the membrane.

Cultured myocardial cells, placed in normal growth medium containing FITC-dextrans, fluorescent molecules to which the membrane is not normally permeable, were subjected to 6-5 ms, rectangular wave electric field stimuli having intensities of 0 V/cm (control), 100 V/cm, or 200 V/cm. Dextran sizes were nominally 4K, 10K, 20K, 40K, or 70K. Ten minutes post-shock, cells were rinsed and photographed (phase and fluorescence) at 40X and 100X (oil-immersion). The resulting photographs were examined for the presence and localization of intracellular marker.

The results demonstrated the intracellular presence of 4K and 10K dextrans following 200 V/cm shocks in 100% (4K) and 83% (10K) of photographs. Dextrans of 20K, 40K, and 70K were excluded. Dextran incorporation correlated with extensive blebbing of the cell surface, with individual blebs exceeding 10u in diameter. In general, dextrans were not incorporated in cells without blebs, or in cells having only "microblebs" less than 10u. Even though the electric field was approximately uniform, dextrans were not incorporated uniformly, but were found primarily in cells from groups with good pre-shock cell-to-cell coupling (which increases effective cell size), and in cells oriented with their long axes in the direction of the field. Following 100 V/cm shocks, 4K dextrans were incorporated in 50% of photographs; 10K dextrans or larger were not incorporated. The 4K dextran incorporation was in cells without membrane blebs.

These results suggest a correlation between increased membrane permeability to macromolecules less than 40A (10K), membrane blebbing, contracture, cell-to-cell uncoupling and depolarization following high intensity electric shock.

Janice L. Jones, Ph.D., Principal Investigator
Ronald E. Jones, M.S.E.E., Collaborating Investigator

BEST COPY AVAILABLE

ARZCO MEDICAL ELECTRONICS, INC.
Swallowable Electrodes for Temporary Cardiac Pacing
GRANT NUMBER: 1 R43 HL 32378-01

Temporary atrial pacing is of value in the management of several arrhythmias, in the termination of supraventricular tachycardia, for diagnosis of conduction disorders, and differentiation of mechanisms of re-entry and automaticity. New applications for atrial pacing include stress testing in patients unable to exercise, and elevation and/or control of heart rate during studies of ventricular function, particularly in connection with imaging procedures. Transesophageal atrial pacing offers an alternative to transvenous catheterization and, with the development of an easily swallowed Pill Electrode, has become a simple and non-invasive clinical procedure.

To address the unique requirements of transesophageal pacing we have designed a stimulator that can deliver the current required for consistent capture, typically 15 to 25 mA, and the pulse widths necessary to excite remote tissue, e.g., up to 10 msec. During this study we have added two modifications to our transesophageal cardiac stimulator: a small electrocardiographic amplifier/recorder, and an output wave-shaping circuit. The first modification provides for locating the esophageal electrode after swallowing and for verifying capture during pacing. The second will permit the device to be used in a switched pace/sense operation.

In order to optimize our electrode design we have derived an analytic solution for current densities anywhere in the heart as a function of bipolar spacing and location of the electrode. We have examined three cases of interelectrode spacing: that of the present Pill Electrode (nominally 1.0 cm), a 3.0 cm, and a 6.0 cm electrode. Our conclusions are that the 1.0 cm electrode remains the preferred embodiment with its excellent proximity effect and ease of encapsulation but precise positioning is crucial. The 6.0 cm electrode displays a diffuse current density pattern with little attenuation at remote sites, posing the danger of inadvertent stimulation of the ventricle. The 3.0 cm electrode will tolerate considerable esophageal misalignment without loss of capture and offers an attractive alternative to the closely spaced electrode in clinical situations where a more forgiving electrode may be needed. Because of this feature we have designed a special 3.0 cm electrode which can be compressed to fit within a gelatin capsule and extends upon swallowing to the correct bipolar spacing. Clinical testing will be required to evaluate the new design.

The Pill Electrode may replace cardiac catheterization in a variety of diagnostic and therapeutic applications resulting in out-patient procedures with greatly reduced complexity and cost.

Janice M. Jenkins, Ph.D., Principal Investigator
Robert Arzbaecher, Ph.D., Collaborating Investigator
Charles Yurkonis, M.S., Collaborating Investigator

BEST COPY AVAILABLE

Index of Institutions

BEST COPY AVAILABLE

BLANK PAGE

INDEX OF INSTITUTIONS

ABIOMED	9,86
American Dental Association Health Foundation	3
Arzco Medical Electronics, Inc.	128
Battelle Columbus Laboratories	36
Baylor College of Medicine	35,44,109
Biometric Systems, Inc.	46
Boston University Medical Center	33
Bowman Gray School of Medicine	99,111
Brown University	21
California Institute of Technology	95
Case Western Reserve University	39,42,126,127
Charles Stark Draper Laboratory	86
Children's Hospital Medical Center	8,11,85
Cleveland Clinic Foundation	63,64,68,79,83
Georgia Institute of Technology	110
Gould Incorporated	65
Harvard Medical School	11,17
Hines Veterans Administration Hospital	18
Indiana University	16
Loyola University Medical Center	18
Massachusetts General Hospital	17,86
Mayo Clinic and Mayo Foundation	5,7,102,108
Medical College of Wisconsin	113
MERCOR, Inc.	49
Montreal General Hospital	81
New York State Department of Health	37
Newark Beth Israel Medical Center	125
Nimbus, Inc.	64,68
Novacor Medical Corporation	55,70
Pacific Medical Center	80
Pennsylvania State University	26,75,77,115,118,123
Research Triangle Institute	91
Rice University	28
St. Elizabeth's Hospital	57
St. Louis University School of Medicine	71

BEST COPY AVAILABLE

Scripps Clinic and Research Foundation	20
Sinai Hospital of Detroit	56
Stanford University	41,70,103,107
Texas Children's Hospital	65
Texas Heart Institute	65
Thermedics, Incorporated	53,57,65,66,85
Thomas Jefferson University Hospital	92
Thoratec Laboratories Corporation	74
Tufts New England Medical Center	15
Tufts University	57
University of Akron	25
University of Arizona	19,105
University of California	100
University of Iowa	97,112
University of Michigan	56,119
University of Missouri	124
University of Pennsylvania	4,98,116,117
University of Pittsburgh	104,114
University of Tennessee	34
University of Texas	43
University of Toronto	38
University of Utah	30,32,82,96,120
University of Washington	31,40,45,63
University of Wisconsin	106
Utah Biomedical Test Laboratory, Inc.	84
Washington University	27
Whalen Biomedical, Inc.	63

BEST COPY AVAILABLE

* U.S. GOVERNMENT PRINTING OFFICE: 1984-461-320:4844